

How early should prevention of adult chronic diseases start?

The developmental origins of chronic disease.

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(Presenter has no conflict of interest to disclose.)

Objectives:

- Describe the developmental origins of health and disease (DOHaD).
- Define the Life Course Theory (LCT) as the framework to understand and develop interventions to maintain and improve reproductive-aged women's health.
- Appraise the value of preconception healthcare within the LCT framework to reduce of the risk of adult chronic diseases.

Outline:

1. Why we are concern.
2. From the Fetal Origins of Adult Disease (**FOAD**) to the Developmental Origin of Health and Disease (**DOHaD**) to explain the occurrence of adult chronic disease.
3. The Life Course Theory of health and disease (**LCT**) framework.
4. Defining preconception healthcare as a primary health strategy to prevent adult chronic diseases.

From the Fetal Origins of Adult Disease (FOAD) to the Developmental Origin of Health and Disease (DOHaD):

FOAD: Barker's hypothesis

- Dr. Barker's studies
- European birth cohorts and registries (Famine in Holland, Leningrad siege)
- Events/exposures during early fetal development
- Animal models and human studies confirm

**Developmental
Plasticity**



LBW as marker of baby health and adult health and disease:

CHD

Metabolic syndrome

Insulin Resistance
(Type II diabetes mellitus)

Obesity

HTN

Cancer

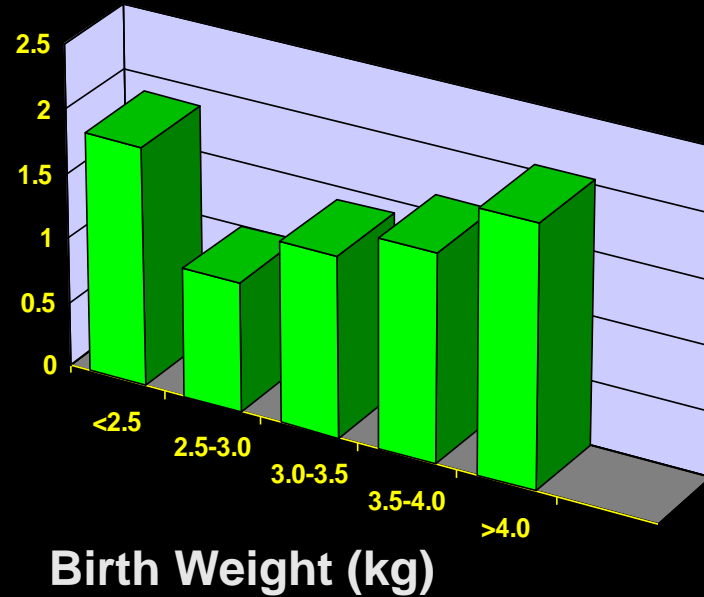
Mental disorders

(Barker et al., 1988, 1989, 1993, 2005, 2007; Hales et al., 1991, 1992; Osmond et al., 1993; Roseboom, 2011; Lumey, 1992; Bateson, 2004)

Obesity in Young Men after Famine Exposure in Utero and early Infancy (Ravelli et al NEJM, 1976)

- N=300, 000 Dutch military inductees at age 19
- Famine exposure in first 2 trimesters lead to 80% higher prevalence of overweight ($p<0.0005$)
- Famine exposure in last trimester or famine exposure in first 5 months of life associated with 40% lower prevalence of overweight ($p<0.005$)
- The difference with the Leningrad experience ?

**Odds
Ratio
For
Obesity**



**Birth weight affects obesity risk
in adults**

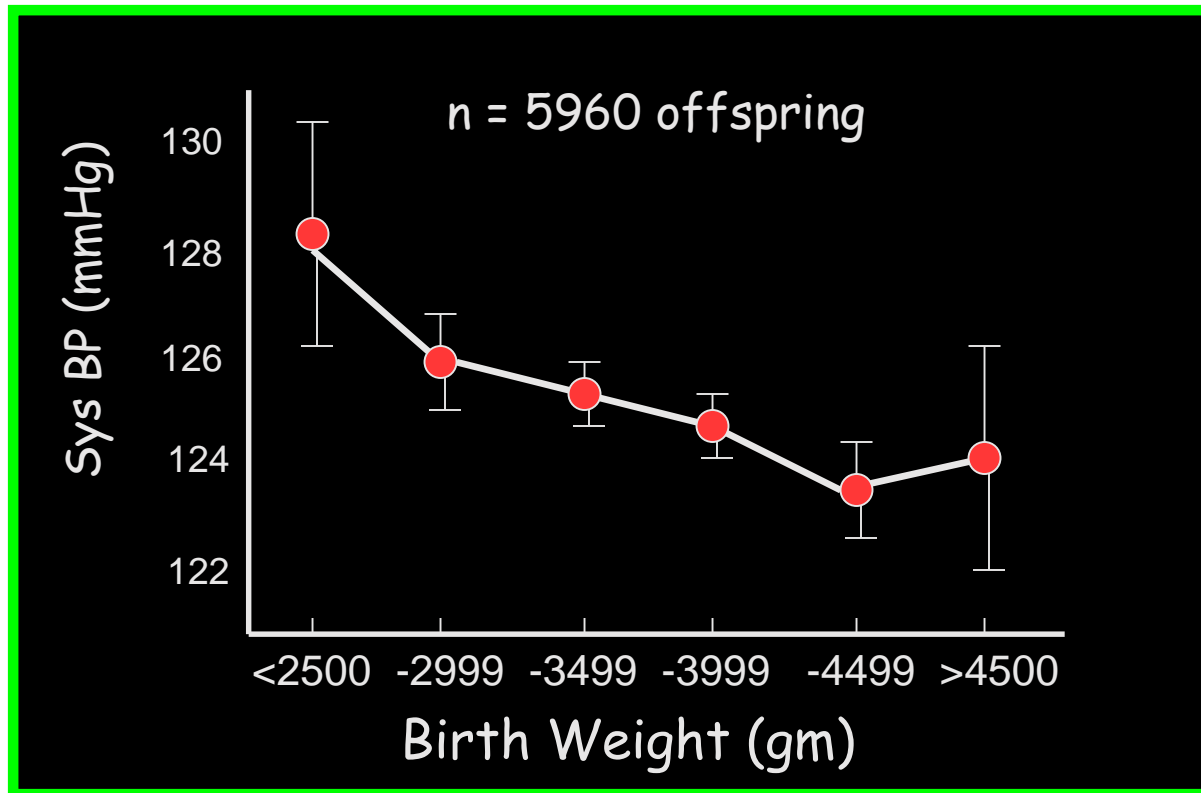
**Trouble arises at Both Ends of
the Birth Weight Spectrum**

(Eriksson et al., 2001)

Birth Weight Predicts Blood Pressure at Age 31

1966 Northern Finland Birth Cohort

+/- adjust for current BMI

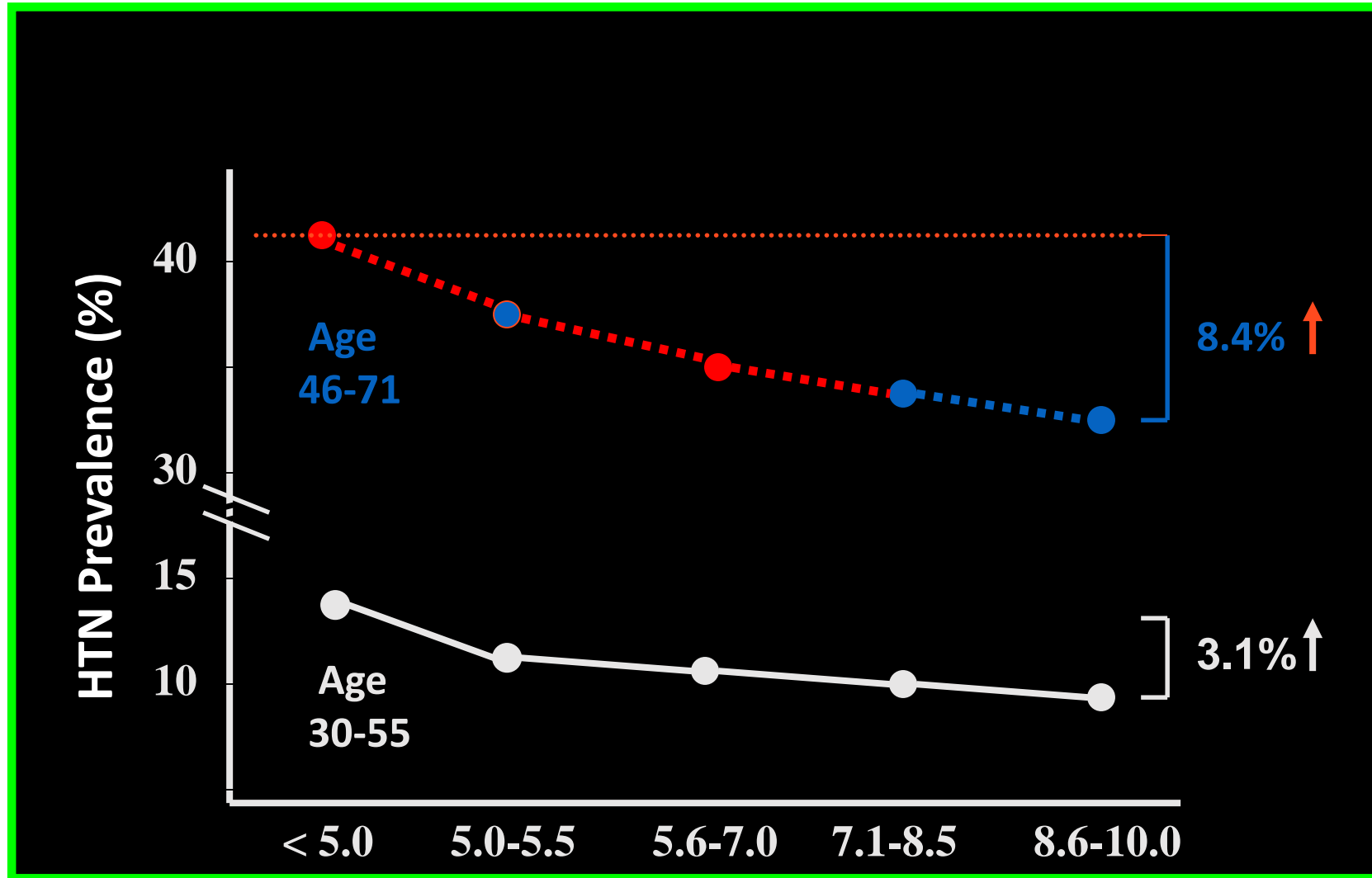


Variables:

Birth Weight
Ponderal Index
Sex
Gestational age
Mat'l Ht, Wt
Parity
Socioeconomic
Current BMI

(Jarvelin et al., 2004)

Birthweight and Adult HTN in US Women



(Curhan et al., 1996 [Nurses Health Study I]; Davies et al., 2006; Hovi et al., 2016)

Implications:

Undernutrition can kill in early life, but it can also lead to a high risk of disease and death later in life. This double burden of malnutrition has common causes: inadequate fetal, infant and young child nutrition followed by exposure (including through marketing practices) to unhealthy energy dense nutrient poor foods and lack of physical activity (catch-up). (U.N Standing Committee on Nutrition, 2006)

Coronary heart disease, stroke, type 2 diabetes, hypertension and osteoporosis, originate through developmental plasticity, in response to malnutrition during fetal life and infancy. Certain cancers, including breast cancer, also originate in fetal life. (Barker DJP. The origins of the developmental origins theory. J Intern Med. 2007.)

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

Low Birth Weight, Low Nephron Number and HTN

"... retardation of renal development as occurs in individuals of low birth weight gives rise to increased postnatal risks for systemic and glomerular hypertension as well as enhanced risk of expression of renal disease."²

(Brenner et al., 1988, 1994)

Developmental Plasticity and “thrifty phenotype” hypothesis:

- ***Susceptible periods*** early during pregnancy
- ***Intrauterine events and exposures***, nutritional and non-nutritional factors
- Developing baby ***plasticity/remodeling***
- Evolutionary advantage of “***plasticity***” ***is lost*** with time, and health problems will arise depending on the environment contributions
- Plasticity becomes ***programming of permanent changes in set-points*** that persist during lifespan

(Bateson, 2004)

‘Thrifty phenotype’ hypothesis (Hale & Barker 1992):



In utero compromised prenatal nutritional environment leads to adjusting organ growth to **spare the brain**, at the cost of other organs and later disease (i.e.: type 2 diabetes and high blood pressure)

- Type 2 diabetes: costs >100 billion\$ annually in USA, *expanding exponentially in developing world (esp. Asia)*, considered an ‘environmental epidemic’; increasingly-prevalent in younger Individuals
- Part of ‘metabolic syndrome’ (obesity, hypertension, type 2 diabetes)

Potential Mechanisms of Developmental Programming

Structural Deficits → Reduced Functional Units in Organs

Kidney	↓ Nephron #	HTN
Pancreas	↓ Islet Cell #	Δ Insulin secretion ↑ Glucose
Muscle	↓ muscle mass	↓ Basal met rate ↓ Exercise capacity
Heart	↓ myocyte #	↑ Risk CHF
Liver	↓ cells #	Δ lipid metabolism

Maternal Protein Deficiency

Asymmetric Growth Restriction in Utero

**“The Thrifty
Phenotype”**

**Impaired Kidney
Development**

**↓ # Nephrons
(permanent)**

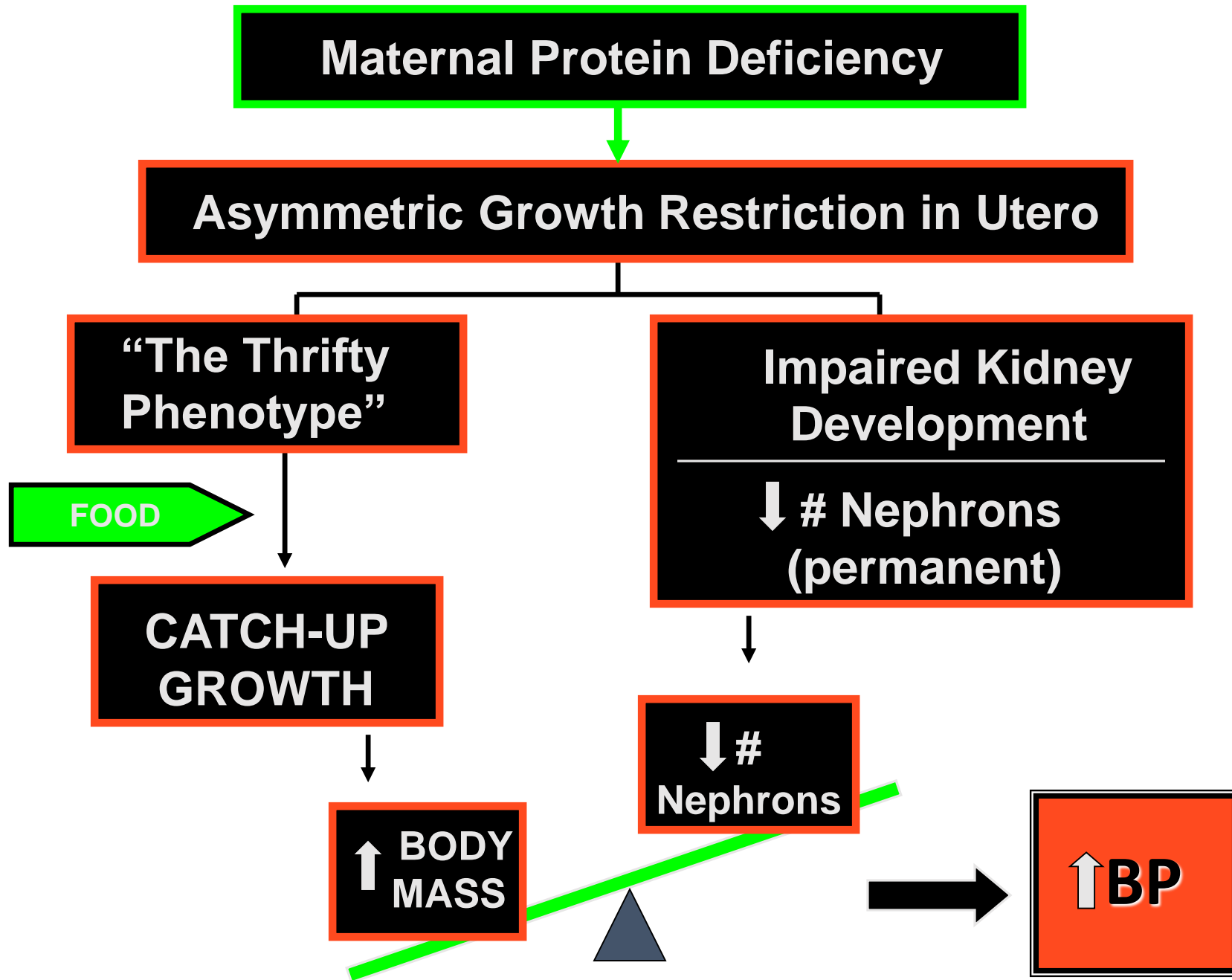
FOOD

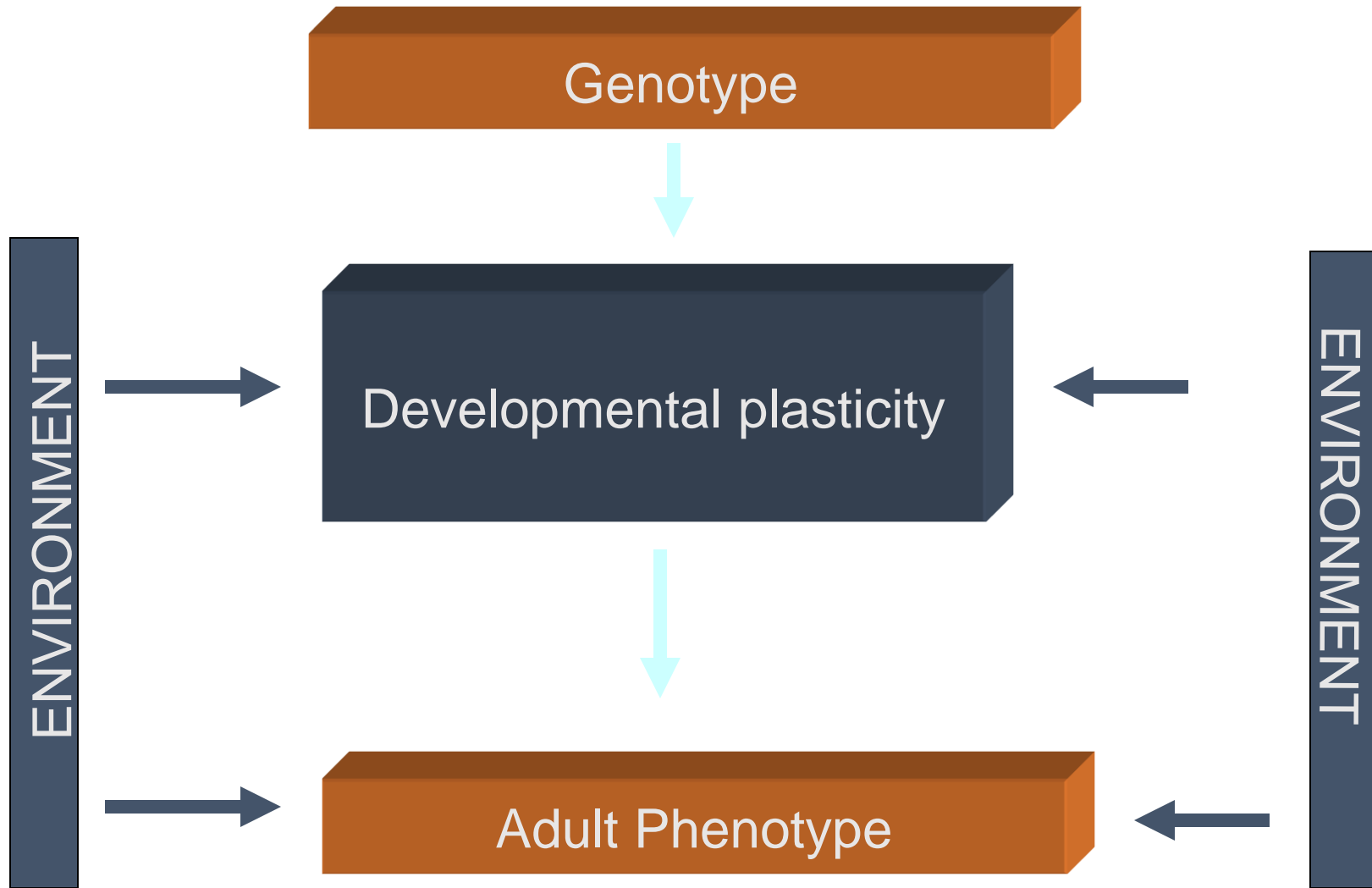
**CATCH-UP
GROWTH**

**↓ #
Nephrons**

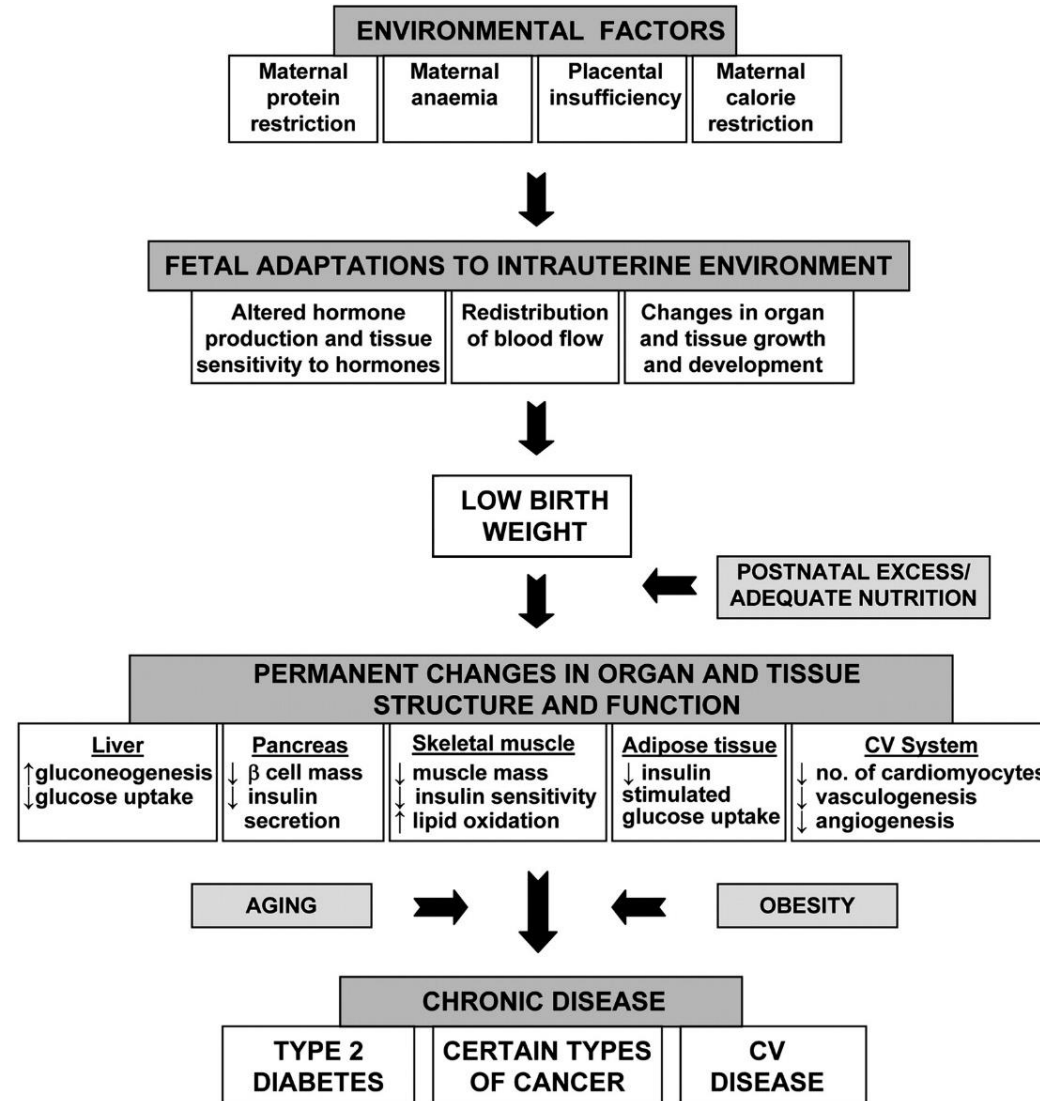
**↑ BODY
MASS**

↑ BP



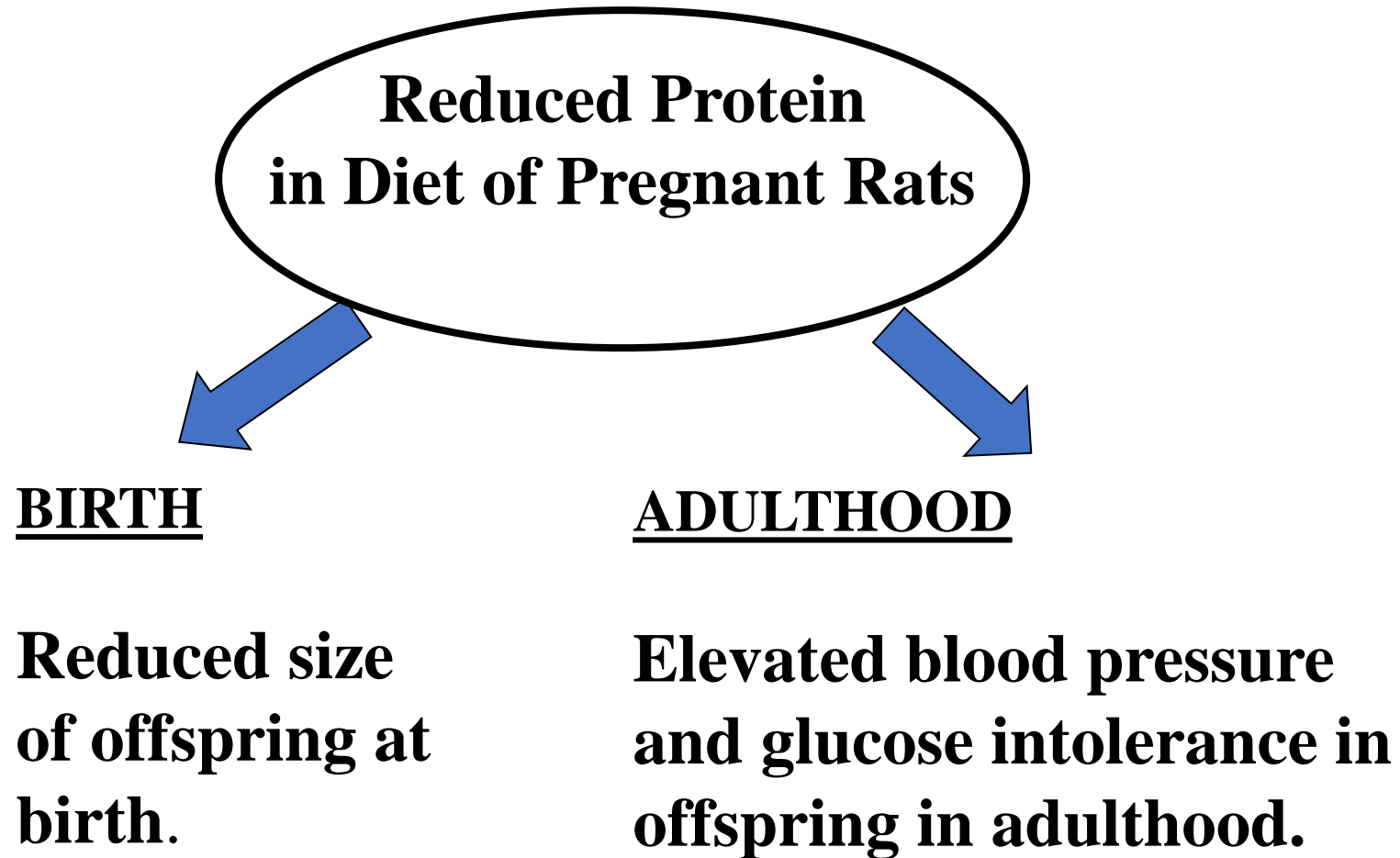


Developmental programming of type 2 diabetes and cardiovascular disease.



Martin-Gronert M S , Ozanne S E J. Nutr. 2010;140:662-666

Animal Studies



Dahri S, et al. *Diabetes* 1991;40:115-20.

Langley SC, et. al. *Clin Sci* 1994;86:217-22.

Transgenerational effects of programming:

Poor baby development → Poor development of organ systems, including reproductive systems → Poor ability to nourish own baby → Poor own baby development



- A mother's exposure to famine prior to conception of her offspring was associated with lower self-reported measures of mental health and quality of life in her adult offspring. (**Stein et al. Epidemiology. 2009 Nov;20(6):909-15**)
- Children born to women with a history of exposure to famine while they were in utero have increased neonatal adiposity and poor health, 1.8 time more frequently, later in life (95% CI 1.1-2.7). (**Painter et al. BJOG, 2008 Sep;115(10):1243-1249**)

So what is Programming:

- * The process through which a *stimulus* or *insult* establishes a *permanent* response
- ** Exposure during a *critical period* in development may influence later metabolic or physiological functions in adult life

Ten Principles of Programming:

- (1) In pregnancy, there are **critical periods of vulnerability** to suboptimal conditions.
- (2) Programming has **permanent effects** that alter responses in later life.
- (3) Fetal development is **sequential and activity dependent**.
- (4) Programming involves several different **structural changes in important organs**.
- (5) The **placenta** plays a key role in programming.
- (6) **Compensation carries a price**. In an unfavorable environment, the developing baby 'makes attempts' to compensate for deficiencies.
- (7) Attempts made to reverse the consequences may have their own unwanted consequences.
- (8) **Fetal cellular mechanisms often differ** from adult processes.
- (9) Programming can have **different effects in males and females**.
- (10) The **effects of programming may pass across generations**.

European Journal of Clinical Nutrition (2004) 58, 438–448
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www.nature.com/ejcn

ORIGINAL COMMUNICATION

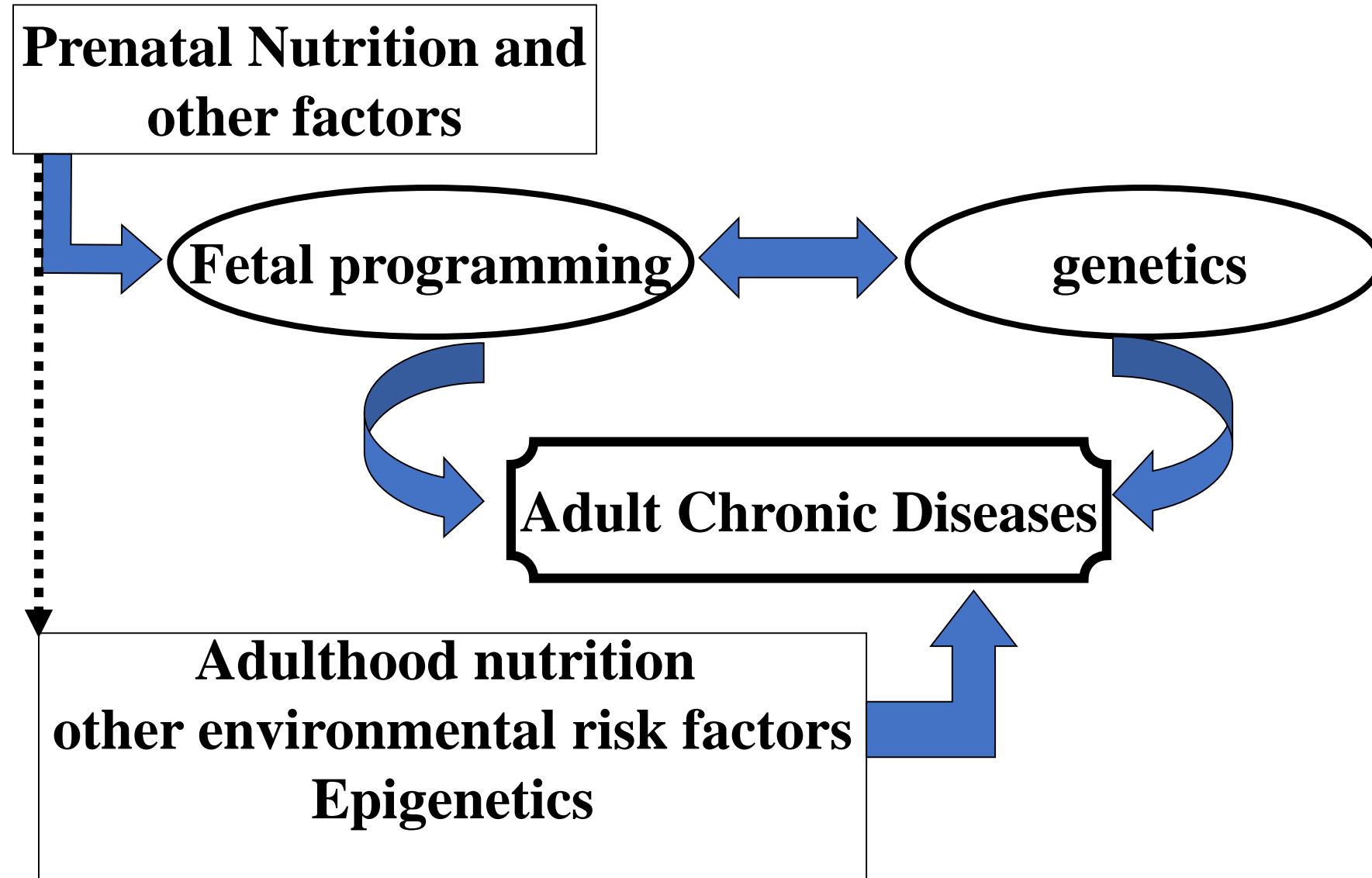
A supply–demand model of fetal energy sufficiency predicts lipid profiles in male but not female Filipino adolescents

CW Kuzawa^{1*} and LS Adair²

Epigenetics: stable alterations in gene expression during development and cell proliferation. Does NOT change the genetic sequence, but modulates when and at what level genes are expressed. (Zeisel, 2009)

- “Epigenetic code is a series of marks added to DNA or to proteins (histones) around which DNA is wrapped.” Methylation, covalent modifications of histones and chromatin and RNA
 - Some “marks” can be inherited
 - Examples of the impact of this inheritance:
 - Grandmother’s smoking in pregnancy & risk of asthma in grandchildren
 - Brains from suicide victims, methylation of 5’ regulatory region of genes encoding ribosomal RNA associated with early childhood abuse & neglect
- (Sandovici et al., 2011)

Integrating hypotheses



WHO - 2000

The implications for training of embracing

A Life Course Approach to Health

International Longevity Centre – UK – London (www.ilcuk.org.uk)

World Health Organization Non-Communicable Disease and Mental Health Cluster Health Promotion, Non-Communicable Disease Prevention and Surveillance Department
www.who.int/ageing

- “...A life course approach emphasizes a temporal and social perspective, looking back across an individual’s or a cohort’s life experiences or across generations for clues to current patterns of health and disease, whilst recognizing that both past and present experiences are shaped by the wider social, economic and cultural context. In epidemiology, a life course approach is being used to study the physical and social hazards *during gestation, childhood, adolescence, young adulthood and midlife that affect chronic disease risk and health outcomes in later life*...(Kuh and Ben-Shlomo, 1997).”
- “...A life course approach incorporates, but is broader than, the fetal origins hypothesis’ (programming) which links conditions in the intrauterine environment to the later development of adult chronic disease (Barker, 1998). ... there are critical periods of growth and development, not just in utero and early infancy but also during childhood and adolescence, when environmental exposures do more damage to health and long-term health potential than they would at other times. “

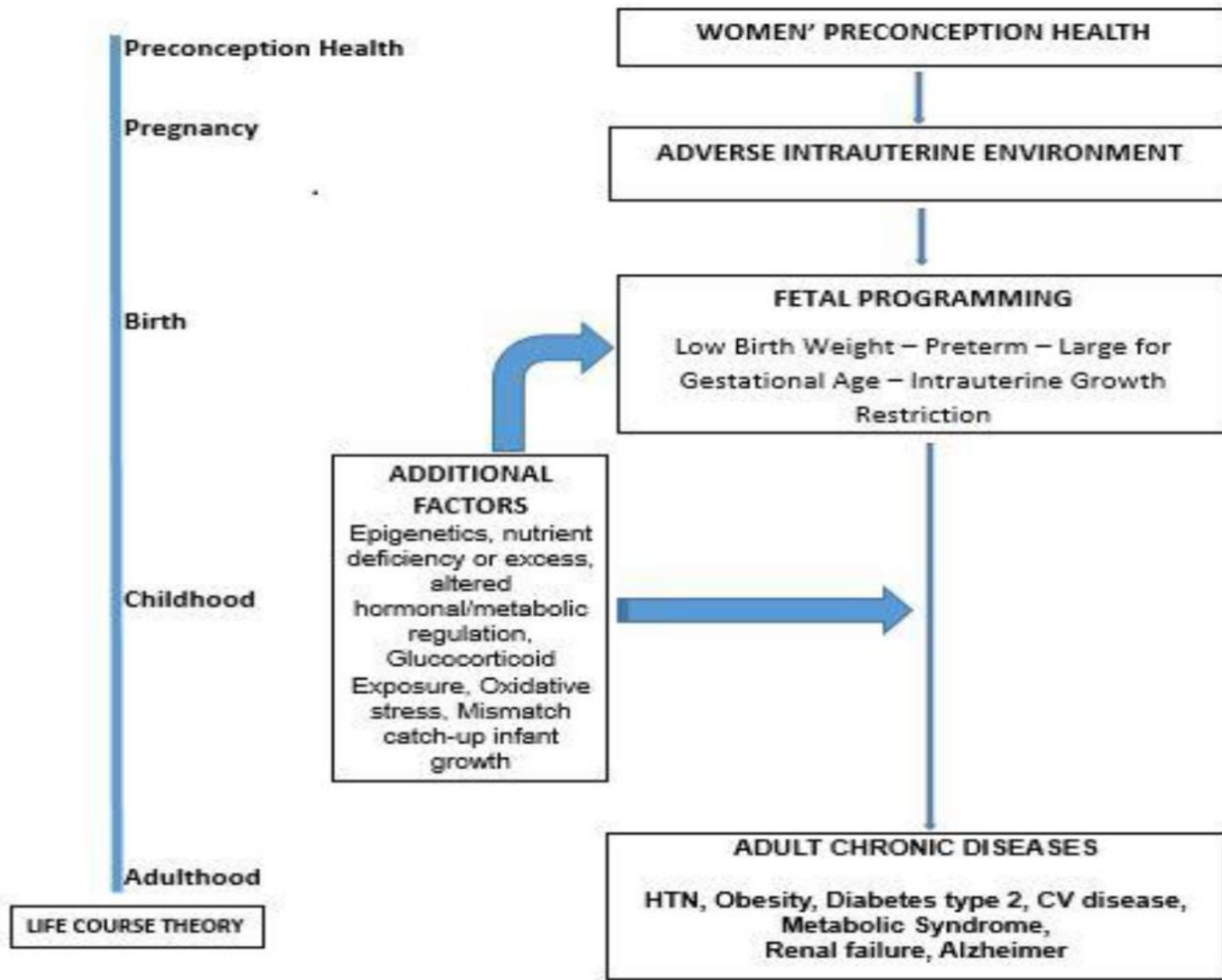


Figure 1. Integrated framework of health and disease: Barker Hypothesis/ Fetal Origin of Adult Disease/Development Origins of Health and Disease/ Life Course Theory of Health. (Adaptation from Brenneke et al. 2013; Paneth 2015)

Life Course Theory of health: a framework explaining health and disease across the lifespan. (Cheng, T. L., Solomon, B., 2014)

Developmental Origin of Health and Disease: adverse exposures early in life, particularly related to women's health and pregnancy outcomes are associated with increase risk to chronic disease susceptibility in adulthood. (Brenneke, B. et al., 2013)

Implications of fetal programming for public health

(1) **Improve the health of young women** - size and health of baby depend in part on status of mother before & after conception

(2) **Focus on populations at highest risk** (evolved in low-nutrition conditions, now in high-nutrition conditions) need to be recognized and informed

(3) **Individuals at highest risk were born small and/or skinny but underwent fast compensatory growth;** interventions for low birth weight should take account of these data

(4) **Transgenerational effects impose special urgency to act soon**



PRECONCEPTION HEALTHCARE = PRIMARY HEALTHCARE = PREVENTION AND HEALTH PROMOTION

“Promotion of the health and well being of a woman
before pregnancy” (Ceffalo R 1995)

“Set of interventions that aim to identify and modify
biomedical, behavioral and social risks to a woman’s
health or pregnancy outcome through prevention and
management” (Kent, et.al, 2006 - Select Panel on Preconception Care; CDC-
MMWR)

Table 1. Recommendations to improve women's preconception healthcare*

Reproductive-life planning**

High blood pressure

Folic acid supplementation

Rubella immunity

Hepatitis B vaccination immunity

Overweight and obesity

Underweight

Anemia

Tobacco and Alcohol use**

Illegal drug use**

Prescription drug use (isoretinoids, anti-epileptics, oral anticoagulants, blood pressure drugs)

Family hx. genetics

Diabetes and diabetes control

Hypothyroidism

Phenylketonuria (PKU)

HIV/AIDS

Sexually transmitted infections (Chlamydia, gonorrhea, syphilis)**

Zika virus**

Environmental chemical exposures, includes occupational**

Mental health -Physical and emotional abuse

*MMWR – Recommendations and Reports-Center for Disease Control and Prevention (CDC 2006, 2012, 2017)

**Female and Male recommendations

Background

- 1. Adverse pregnancy outcomes, higher IMR, rising maternal mortality and health disparities**
- 2. Prenatal care shortcomings**
- 3. Prevalence of unintended pregnancies**
- 4. Women's health risk behaviors and lifestyle**
- 5. Evidence based strategies to improve pregnancy outcomes**

(Alexander G 2001; Rosenberg 2003; Floyd L 2007; Moos MK, 2004; Naimi T 2002; Lumley J Cochrane

Review 2002; CDC-Ntl. Center for Health Stats - <https://www.cdc.gov/nchs/pressroom/states/southdakota/southdakota.htm>)

Risk behaviors in reproductive-aged women

- Sd PRAMS 2016: 57.5% not pregnancy planning, not contraception
- overweight/obese
- alcohol
- smoking
- folic acid
- chronic condition/s
- **Evidence-based interventions exist**



- Preterm birth
- Low weight babies
- Large babies
- Birth defects
- Sudden infant death
- Infant Mortality
- Maternal complications

“Understanding Women’s Preconception Healthcare Awareness and Access in a Midwestern Rural State”

(Lammers et al; 2017)

Most women (83%) saw a health provider the year before the survey, but only 54% had a conversation about PCHC.

Preconception healthcare awareness was significantly lower among women without health insurance (95%ci=1.05, 1.81), single (95%ci=1.03, 1.60), and had lower education (95%ci=1.01, 1.61).

Race other than White and lack of preconception health awareness contributed to receiving fewer services.

Overall, 74.6% received three or fewer of the preconception services known to improve perinatal outcomes.

What did we learn from our assessment?

- Despite good evidence of the benefits on pregnancy outcomes **women lack preconception healthcare awareness.**
- **Preconception healthcare is NOT** part of the routine care provided to reproductive-aged women in most clinical settings.
- ***“Ask every woman” should become the mantra of primary healthcare for reproductive-aged women—every woman of reproductive age should be asked about her reproductive plans, and be informed about their risk of unintended pregnancy and how risks behaviors can have adverse effects on pregnancy even before they know are pregnant.*** (Bernstein, 2005)
- Lack of RCT implementing the whole set of PCHC interventions, but there is enough evidence of the benefits of the individual PCHC interventions to **support including preconception care in the routine care of all reproductive-aged women.**

Next step: focus on women
awareness and education...

“Increasing rural women’s preconception healthcare knowledge and self-efficacy: A quasi-experimental pilot study.”

(Lammers, Jenson, Stluka, Wilson-Wiebe & Zastrow, 2014)

OBJECTIVES

Develop and implement a community-based PCHC educational program that follows the HBM

Demonstrate an increase in PCHC knowledge and self-efficacy among rural reproductive-aged women

METHODS

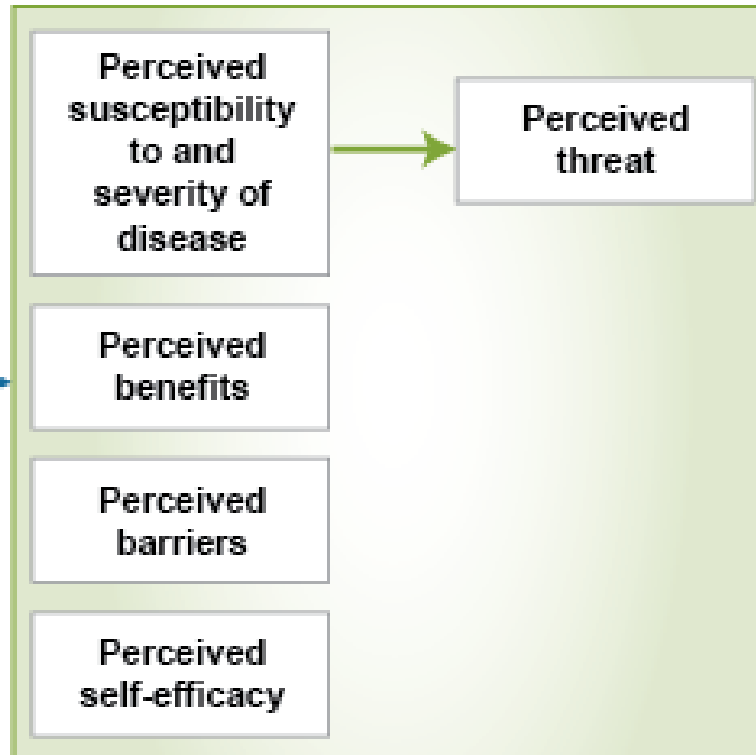
- ✓ Quasi-experimental 2 groups pre-posttest design was used
- ✓ 85 women ages 18-45 participated (44 comparison-41 study); small towns and rural areas
- ✓ Questionnaires (Likert scale) to assess PCHC knowledge and self-efficacy were validated (Cronbach alpha ranged .529 - .810)
- ✓ Intervention educational protocol was developed, that focused on the HBM constructs (2 sessions)

HEALTH BELIEF MODEL CONSTRUCTS

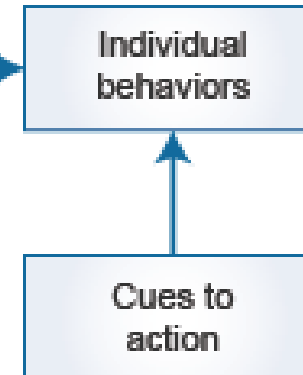
Modifying Factors

Age
Gender
Ethnicity
Personality
Socioeconomics
Knowledge

Individual Beliefs



Action



Source: Glanz K, Rimer BK, Viswanath K, eds. 2008. *Health Behavior and Health Education: Theory, Research, and Practice (4th ed)*. San Francisco: Jossey-Bass. <http://www.esourceresearch.org/Default.aspx?TabId=731>

Results:

- ✓ Pre-post intervention within the study group showed significant increase in **PCHC knowledge (p=.021) and the HBM summary score (p=.009)**
- ✓ Between comparison and study groups results also showed **significant improvement in PCHC knowledge (p<.001) and in the HBM summary score (p=.015)**
- ✓ HBM subscale analysis showed **significant increase in risk perception (p=.010), severity (p=.041), self-efficacy (p=.015), and cue for action (p=.007) in the study group**

In summary:

- ✓ PCHC relevant to the Life Course Theory of Health
- ✓ Enough evidence supports the benefits of individual preconception health interventions that improve pregnancy outcomes, reduce infant and maternal deaths, and the risk of adult chronic disease
- ✓ Preconception healthcare is an underutilized preventive and health promotion care intervention
- ✓ Despite study limitations, findings support providing preconception healthcare education to women using the HBM framework to increase their knowledge and empower them to take action
- ✓ Further research to identify additional strategies to increase PCHC knowledge among women and best evidence of providing comprehensive PCHC to all reproductive-aged women

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Thank you!

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