

Early Origins of Metabolic Disease and Aging

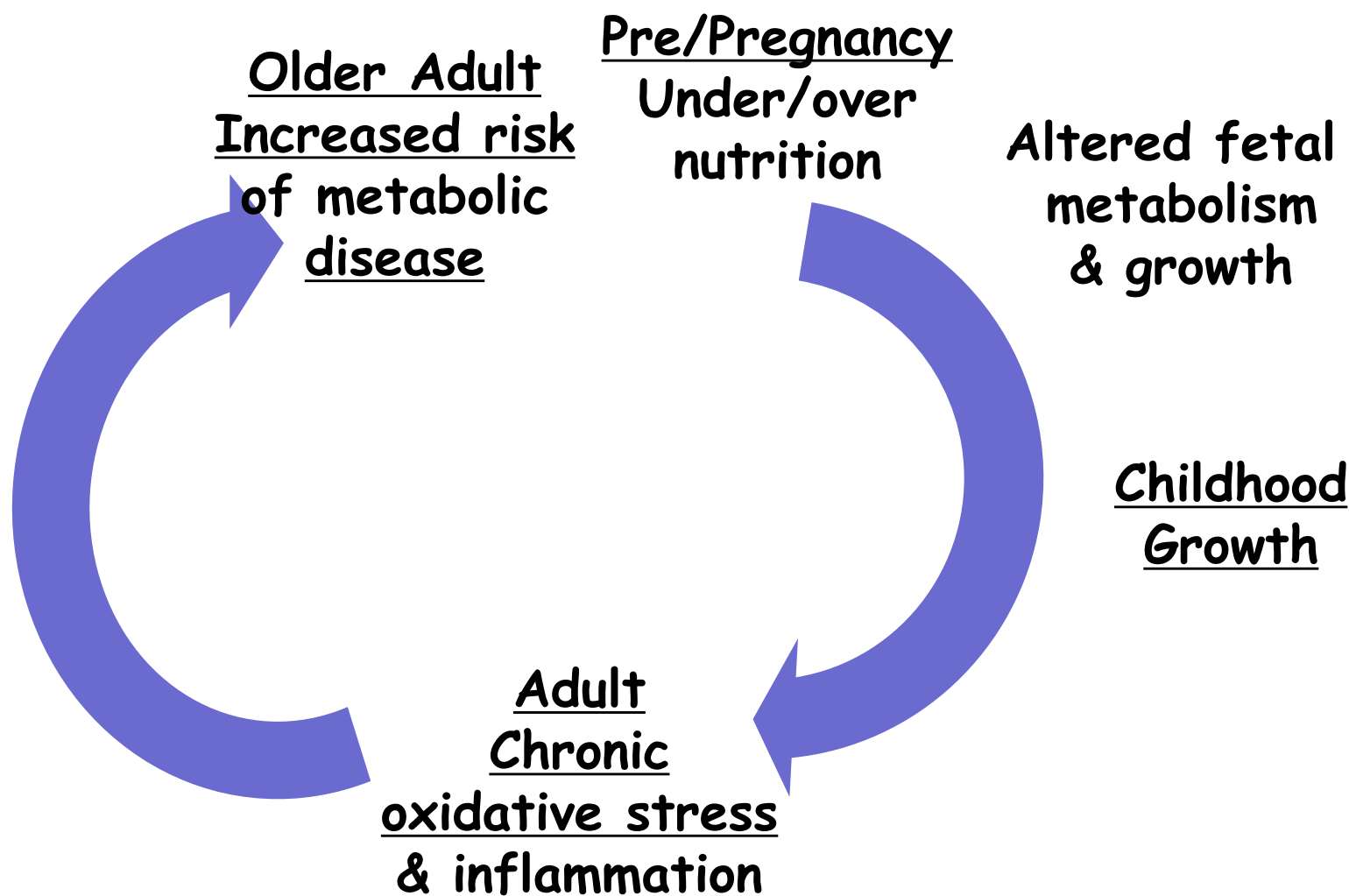
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The Maternal Nutrition-Offspring Metabolic Disease Cycle



First Evidence Linking Fetal Nutrition & Later Health

Dutch Famine during WWII:

- Natural study of severe food deprivation
- Embargo of Amsterdam from December, 1944-April, 1945 (6 months)
- Rations provided 400-800 kcal/d; protein limited to 30-40 g/d.
- Liberated May 5, 1945: food supply immediately increased to ~2000 kcal/d
- Result: maternal starvation imposed at different stages of pregnancy

Severe starvation at different stages of pregnancy caused different outcomes,

Susser M. Nutr Rev 1994;52:84-94

Periconception	First Trimester	Third Trimester
Infertility Increased neural tube defects Increased schizophrenia Antisocial personality	Pre-term births Stillbirths First week deaths Increased obesity later in life	Low maternal weight gain Reduced birth weight in 1 st and 2 nd generations Increased neonatal mortality (0-3 mo) Decreased obesity

*Each period of fetal development is dependent on nutrition.
Changes irreversible.*

Barker Hypothesis: Fetal Origins of Adult Disease

1986: Barker and his colleagues reported that malnutrition in the womb changes the structure and function of the body for life making the individual vulnerable to heart disease, diabetes, and stroke.

Called fetal programming.

2004: International Society for Developmental Origins of Health and Disease (DOHaD) formed.

2010: DOHaD scope expanded to include gestational exposure to overnutrition and stress.

Barker's Initial Paper

Infant Mortality, Childhood Nutrition, and Ischaemic Heart Disease in England and Wales, Lancet. 1986

- Analyzed large birth cohort studies from different regions of England and Wales.
- Strong geographic relationship occurred between IHD mortality rates and infant mortality 40 years earlier.
 - Higher infant mortality rates in 1920s associated with elevated IHD in 1960s.
 - Poor rural areas had higher rates of infant mortality and IHD than urban areas.
- Relationship between infant mortality and other diseases was not as strong.

Conclusion: Poor nutrition in early life increases later susceptibility to the effects of an affluent diet.

Fetal & Childhood Origins of Adult Disease,

Barker et al., Int J Epidemiol 2002;31:1235

- Helsinki Cohort: 13,517 men and women born 1924-44.
 - Birth, childhood, and adult disease data available from hospital records.
- Disease risk increased with a low birth weight plus a marked increase in childhood BMI from 3-11 years.

Net increase in chronic disease compared to infants with normal birth weight and childhood growth

Type 2 Diabetes	↑ 57%
Hypertension	↑ 25%
Coronary Heart Disease	Men ↑ 25% Women ↑ 63%

Fetal Origins of Adult Disease

Conclusions

- **>100 studies performed involving ~500,000 cases**
- **Low birth weight consistently associated with type 2 diabetes, hypertension, dyslipidemia, central obesity, insulin resistance, and CVD in adults.**
- **Inconsistent relationship with respiratory, immunity, cancer, or psychiatric illnesses.**
- **Brain growth is 'protected' at the expense of lung, heart, and kidney tissue.**

Early Life Programming Models

Fetal	Childhood (≥ 3 years)
Under nutrition	Under nutrition
Under nutrition	Over nutrition
Over nutrition	Over nutrition

Maternal Obesity and Offspring Development,

Gaillard, R., Eur J Epidemiol 2015; 30:1141.

Fetal Outcomes	Childhood Outcomes	Adult Outcomes
Stillbirth Neonatal deaths Congenital anomalies Large for gestation age Neonatal hypoglycemia Referral to ICU	Obesity Adverse body composition Increased blood pressure Adverse lipid profile Increased inflammatory markers Impaired insulin/glucose homeostasis	Obesity High blood pressure Adverse lipid profile Impaired insulin/glucose homeostasis Premature mortality

- Maternal pre-pregnancy obesity more strongly associated with adverse fetal outcomes than GWG.
- Maternal obesity alters placental structure and function that increases later disease risk.
- Excessive first trimester weight gain a key factor for an adverse later cardio-metabolic profile.

Breast-feeding and Later Health

- Difficult to determine breastfeeding exposures.
- Data are primarily from higher income countries.

Preliminary Conclusions

1. In high-income populations, breastfeeding is associated with reductions in blood pressure, blood cholesterol, and a lower risk of obesity and diabetes as adults. Robinson S and Fall C. *Nutrients* 2012;4:859
1. Early exclusive breastfeeding (4-6 wk) is associated with longer telomeres at 4-5 yrs of age. Wojcicki JM et al., *AJCN* 2016;104:397.

What mechanisms link early nutrition and later health?

DNA methylation (i.e., epigenetics) could silence a gene and increase disease risk.

- **Maternal micronutrient intakes:**

(folate, methionine, B12, choline, B6, riboflavin)

- **Microbiome:**

The Mother's microbiota may produce metabolites with epigenetic (methylation) potential.

Maternal Nutrition & DNA Methylation

Randomized Gambian women to a multi-micronutrient or placebo supplementation from pre-pregnancy to the end of the first trimester. Cooper, WN et al. FASEB J 26:1782. 2012.

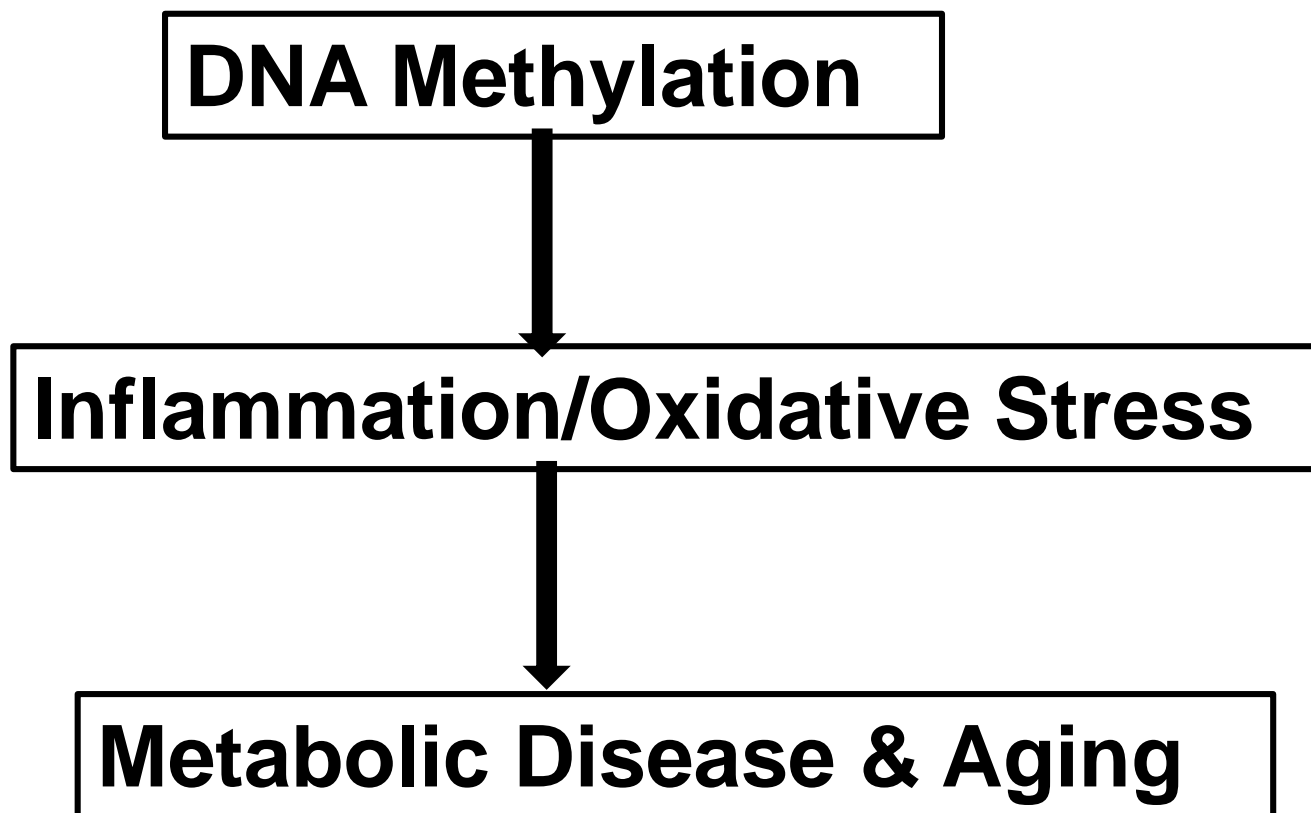
- **Periconceptional nutrition influenced methylation of genes in the newborn**
- **Genes methylated differed between boys and girls.**
- **Methylation occurred independent of the season of the year.**

Confirmed: Maternal diet can influence the methylation of genes in the newborn.

Gambian Study of Maternal Diet, Biomarkers of Methylation, & Infant Gene Methylation, Dominguez-Salas P et al., AJCN, 2013;97:1217 & Dominguez-Salas P et al., Nature Comm 2014.

- Seasonal variations in dietary intakes of methyl-donors.
 - Rainy season—hungry period
- Blood biomarkers of methylation (folate, methionine, riboflavin, and SAM/SAH ratio) higher during the rainy season.
- Offspring of rainy season conceptions had higher levels of leukocyte and hair DNA methylation.
- Higher maternal BMI predicted less DNA methylation.

Conclusion: Poor maternal nutrition at conception enhances gene silencing in newborns.

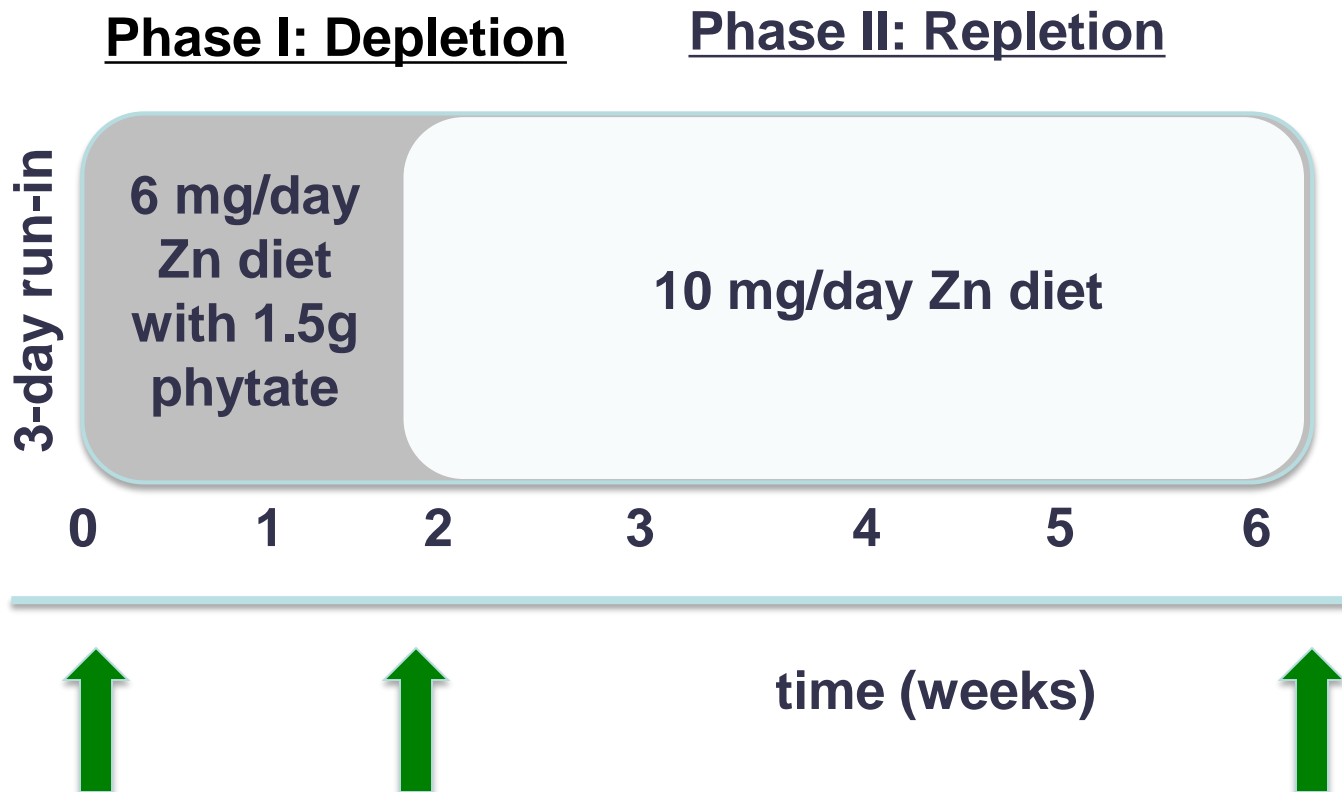


Nutrition, Inflammation & Aging

The Triage Theory. Ames, BN. PNAS. 2006, 103;17589.

- **Micronutrient deficiencies cause DNA damage due to oxidative stress and/or inflammation.**
- **May also cause mitochondrial decay and cellular aging.**
- **Natural selection favors short-term survival at the expense of long-term health.**
- **Ho: With micronutrient deficiencies essential nutrients are triaged to support critical functions. This shift reduces the availability of micronutrients to prevent oxidative stress and inflammation.**

Do small increases in diet zinc reduce DNA damage?

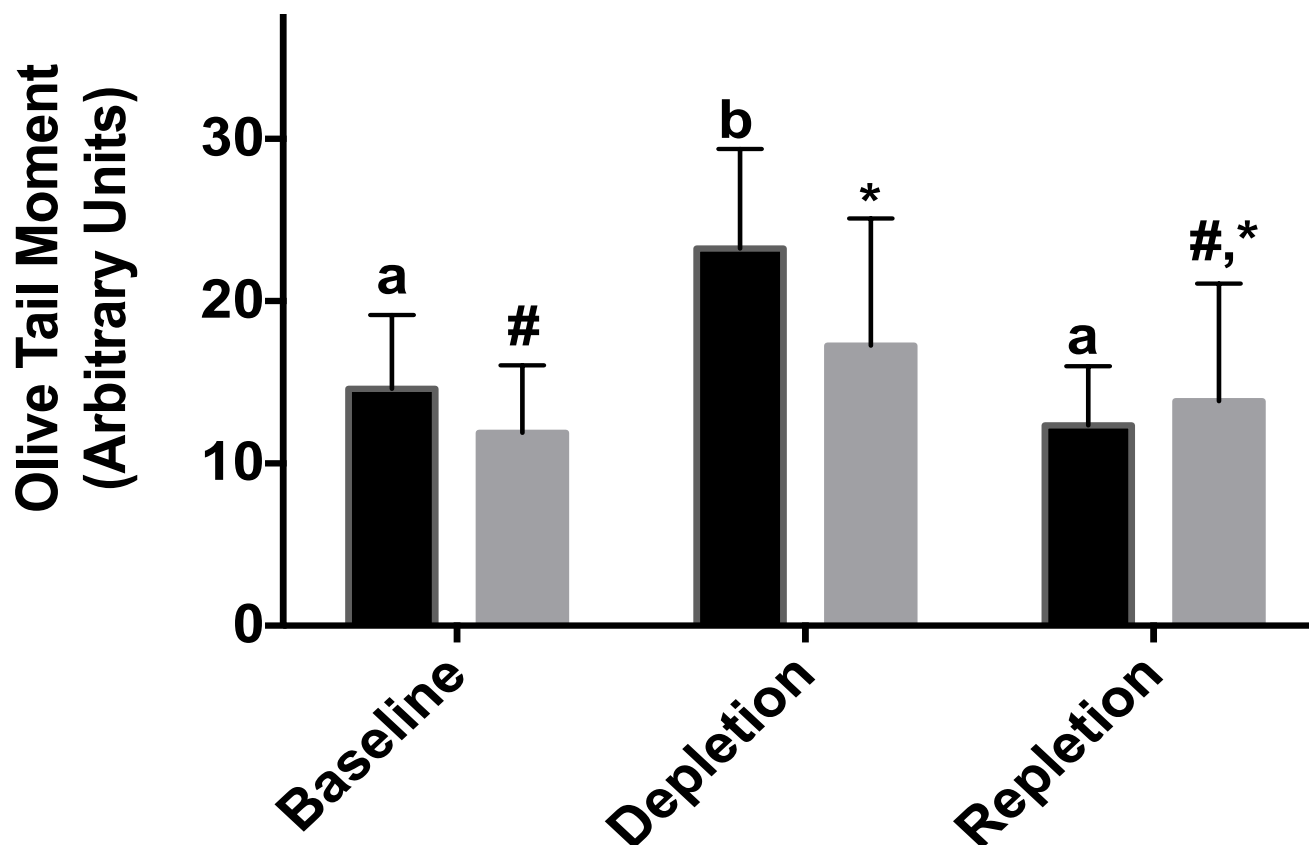


18 men
Controlled diet

BLOOD DRAWS

Diet: 80% CHO
10% protein
10% fat

Zinc Reduces DNA Damage



Black: DNA strand breaks (Comet Assay) increased significantly after 2 weeks on the 6 mg zinc diet and declined with 10 mg diet zinc for 4 weeks.
Grey: Oxidized DNA lesions (FPG Assay) increased significantly with low zinc diet for 2 weeks. Non-significant decline with repletion.

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