The Fetal Origins of Adult Disease *or* Why Obstetrics is the Most Important Specialty

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Maternal-Fetal Medicine

The Dutch "Hunger Winter" 1944 - 1945

- All food and fuel transports banned
- Early and severe winter

FAMINE
400-800 cal / day from Dec '44 - April '45

- Liberation May 5, 1945 →
  > 2000 cal / day by June '45

Dutch Famine Study

- 300,000 19-year-old men exposed 1944-45
- Examined at military induction

Exposure in 3rd Δ → Lower Obesity Rate

Exposure in 1st half → Higher Obesity Rate

Ravelli, et al
N Engl J Med
1976; 7:349

Barker Hypothesis

Based on medical archives from Preston, Hertfordshire, and Sheffield, England

16,000 men and women born in Hertfordshire, 1911- 1930:

- 2-fold increase in coronary heart disease from largest to smallest BW
- Impaired GT increased from 14% to 40%

Barker, et al
Clin Sci 1998; 115:118

Death Rates From Coronary Artery Disease According to Birthweight

Birthweight, lb (kg)	Standardized mortality ratio	No. of deaths
≤ 5.5 (2.50)	100	57
–6.5 (2.95)	81	137
–7.5 (3.41)	80	298
–8.5 (3.86)	74	289
–9.5 (4.31)	55	103
> 9.5 (4.31)	65	57
All	74	941

Prevelance of Type II DM and Impaired Glucose Tolerance in Men Age 59-70

Birthweight, lb (kg)	No. of men	% with impaired glucose tolerance or diabetes	Odds ratio adjusted for body mass index (95% confidence interval)
≤ 5.5 (2.50)	20	40	6.6 (1.5 to 28)
–6.5 (2.95)	47	34	4.8 (1.3 to 17)
–7.5 (3.41)	104	31	4.6 (1.4 to 16)
–8.5 (3.86)	117	22	2.6 (0.8 to 8.9)
–9.5 (4.31)	54	13	1.4 (0.3 to 5.6)
> 9.5 (4.31)	28	14	1.0
All	370	25	

Reduced Fetal Growth and Ischemic Heart Disease in Swedish Men

14,611 children born 1915-29, followed until 1995:

- For every 1000 gram ↑ in birthweight, ↓ rate heart disease

  OR 0.77 (0.67 - 0.90)

Leon, et al
BMJ 1998; 317:241

Mean BW for EGA	Death from Heart Disease*
2949 (1080-3520)	1.0
3380 (2230-3790)	0.80 (0.62-1.04)
3664 (2700-4050)	0.61 (0.43-0.86)
4113 (3040-5300)	0.67 (0.43-1.02)

**P = 0.003*

Leon, et al
BMJ 1998; 317:241

The Nurses Health Study

- 121,701 RNs aged 30 - 55 yrs, followed since 1976
- BW self-reported, validated by birth certificate

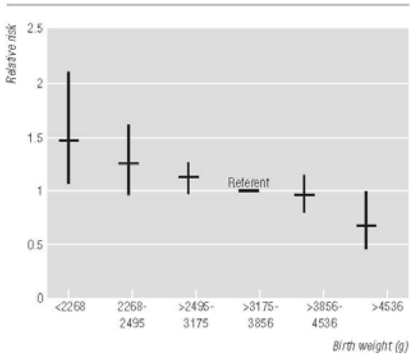
Rich-Edwards, et al
BMJ 1997; 315:396

The Nurses Health Study

	CAD	MI	Stroke
< 2269 g	1.32	1.29	2.29
2268-2495 g	1.15	0.95	1.38
2496-3175 g	1.02	0.92	1.25
3176-3856 g	(ref)	(ref)	(ref)
3857-4536 g	0.92	0.92	0.99
≥ 4537 g	0.68	0.68	0.66

Rich-Edwards, et al
BMJ 1997; 315:396

RR Non-Fatal CV Disease by BW



Thrifty Phenotype Hypothesis

During periods of starvation, the fetus reduces insulin secretion, and increases peripheral insulin resistance, thus directing more glucose to the brain and heart, and less to skeletal muscle, etc.

Hales and Barker
Diabetologica 1992; 35: 595

Organ Systems With Evidence of Fetal Programming

System	Examples
Cardiovascular	Vascular compliance LV thickness Endothelial function
Skeletal	Insulin resistance Glycolysis with exercise
Endocrine	H-P-A Axis Glucose-insulin metab. Growth - IGF-1 Axis Gonadotropic axis

Organ Systems With Evidence of Fetal Programming

System	Examples
Renal	Renin-Angiotensin system
Liver	Cholesterol Metabolism Fibrinogen, Factor VII
Bone	Bone Mineral Content

Organ Systems With Evidence of Fetal Programming

System	Examples
Pulmonary	Lung volumes
Immune system	Thyroid autoantibodies Ig E concentration

Barker Hypothesis

Birth phenotypes associated with later disease:

THIN: Insulin resistant as children and adults

SHORT: Abnormal liver function (↑ LDL cholesterol, fibrinogen)

SHORT AND FAT: Insulin deficient

Arch Dis Child
1999; 80:305

Barker Hypothesis

THIN: Adapted to undernutrition by endocrine and metabolic changes

SHORT: Brain sparing circulatory adaptation

SHORT AND FAT: Maternal hyperglycemia

Arch Dis Child
1999; 80:305

The Dutch Famine Cohort

All term infants born at the Wilhelmina Gasthaus

Nov 1, 1943 → Feb 28, 1947

2414 infants with medical records

912 alive, traceable, agreed to participate (mean age 50 years; 48-53)

Painter, et al
Reprod. Tox
2005; 20:345

Compared to those born before famine:

3rd Δ Exposure: Shorter, Thinner, Smaller HC
Adult BMI = 26.7
Impaired Glucose Tolerance

2nd Δ Exposure: Shorter, Thinner, Smaller HC
Adult BMI = 26.6
↑Obstructive Airway Dz
(OR1.7, 1.1-2.6)
Microalbuminuria
(OR 2.1; 1.0-4.3)

Painter, et al
Reprod. Tox
2005; 20:345

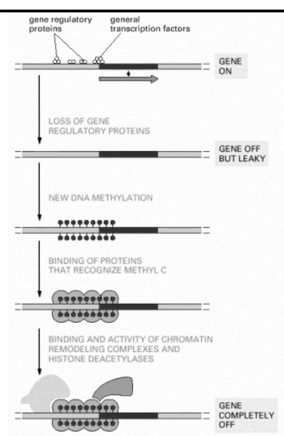
Compared to those born before famine:

1st Δ Exposure: Average size at birth
Adult BMI = 28.1
More Adult Obesity
More Atherogenic Lipid Profile
More Coronary Artery Dz
(OR 3.0; 1.1-1.8)
↑Fibrinogen, ↓Factor VII

Painter, et al
Reprod. Tox
2005; 20:345

Metabolic "Programming" via Genetic Imprinting

- Imprinting turns gene off
- Gene dosage effect- only one gene operational
- Some imprinting reflects gender of transmitting parent
- Many imprinted genes involve metabolism
  i.e. Igf 2 , Igf 2r, H19



Factors Influencing Fetal Development

- Calorie intake
- Carbohydrate and Protein content
- Micronutrients
- Environment (sunlight)
- Stress

Mothers Weight vs Heart Disease in Adult Offspring

- 3302 men born in Helsinki, 1929-33, still alive in 1971 (38 - 42 yrs)
- 286 ultimately died of coronary artery disease (mean age 57)

Forsen, et al
BMJ 1997;
315:837

Birth Weight	Mortality Ratio from CAD
≤ 2.5 K	84
2.6 – 3.0	83
3.1 – 3.5	99
3.6 – 4.0	76
≥ 4.1	66
ALL	85*

Children of laborers = 83
Higher social class = 90

Forsen, et al
BMJ 1997;
315:837

Ponderal Index*	Mortality Ratio from CAD
25.6	111
26.7	98
27.3	76
28.3	66
ALL: 27.0	86

*Ponderal Index = weight / height³

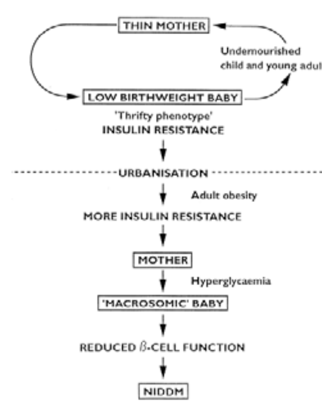
Forsen, et al
BMJ 1997;
315:837

	ALL BMI		Mom's Height < 5'2" BMI		Mom's Height > 5'2" BMI	
Ponderal Index	26	>30	26	>30	26	>30
≤ 25	134	171	106	224	170	71
26-27	87	131	70	134	102	126
28-29	76	116	54	149	97	79
> 29	71	72	63	75	59	70

Forsen, et al
BMJ 1997;
315:837

Why did short fat mothers have offspring with highest rate of CAD?

- Mother's short height reflects in utero deprivation
- Mothers weight reflects postnatal nutrition (↑CHO) and her own metabolic programming



Transgenerational Effects of Dutch Famine

- Adults born during Dutch Famine (1944-45), now age 58 (56 - 61)
- 856 Offspring, age 29-34

If mother exposed to famine as fetus, offspring were shorter (p=.01) and had higher ponderal index (p=.001) at birth

Painter et al
Epidemiol 2008; 115: 1243

Growth Trajectory in Children Who Have Coronary Events as Adults

- Used Helsinki population
- Evaluated BW and BMI at ages 2 and 11 years
- Correlated with adult coronary events

Baker, et al
NEJM 2005;
353:1802

Coronary Events Predicted by:

- Low Birthweight and BMI (p < .001)
- Low BMI at age 2 and
  High BMI at age 11 (p < .001)

Baker, et al
NEJM 2005;
353:1802

Hazard Ratios for Coronary Artery Dz in Adults

	BMI at 11 in Boys / Girls		
BMI at age 2	< 16	16-17.5	>17.5
< 16	1.6 / 1.8	2.4 / 2.5	3.0 / 3.1
16-17	1.4 / 1.7	1.6 / 1.8	1.9 / 2.0
>17	1.0 / 1.0	1.3 / 1.5	1.1 / 1.2

Baker, et al
NEJM 2005;353:1802

Children Born with IUGR (< 2.5K):

↓ Nephron number
Fewer glomeruli
↓ Renal volumes

Adult glomeruli : 1,400,000 / kidney in controls
700,000 / kidney in HTN

Rostand
Nephol Dial Transplant 2003;
18:1434

Mean BP vs Weight at Age 5

- 262 children selected from larger study of recurrent IUGR

  58 IUGR; 202 AGA
- Mothers normotensive, similar rates of GDM, smoking, EtOH during pregnancy
- Evaluated at age 5

Wenstrom et al
AJOG 2005

Mean BP vs Weight at Age 5

Weight	IUGR S	IUGR D	IUGR MAP	AGA S	AGA D	AGA MAP
< 10 %	89*	54*	65*	91	58	69
< 25 %	93	58	70	90	59	69
< 50 %	96	60	72	91	58	69
50-75%	109	60	76	94	58	70

* p <.05

Wenstrom et al
AJOG 2005

Factors Influencing Fetal Development

- Calorie intake
- Protein content
- Micronutrients
- Environment (sunlight)
- Stress

Dutch Famine and Schizophrenia

- Military induction data:
  18 y o males born 1944 - 46
- National Psychiatric Registry
  (> 90% of all psych admits in the Netherlands)

Hoek, et al
Psych Psychiatric Epidemiol
1998; 33:373

- Excess CNS anomalies if first Δ exposure to worst famine (conceived Feb - April 1945)

RR = 2.5 (1.3-4.9)

Hoek, et al
Psych Psychiatric Epidemiol
1998; 33:373

- First Δ exposure to worst famine = increased risk schizophrenia

RR = 2.0 (1.2-3.4) *

Males 1.9 (1.0-3.7)

Females 2.2 (1.0-4.7)

**Proportion of affected relatives unchanged*

Hoek, et al
Psych Psychiatric Epidemiol
1998; 33:373

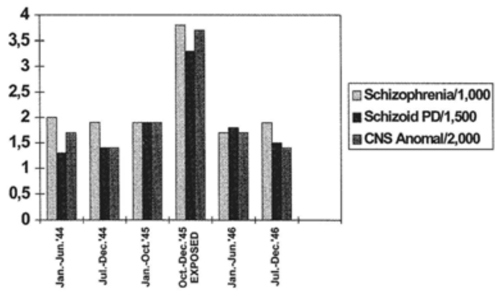
- First Δ exposure to worst famine = ↑ risk schizophrenia spectrum personality disorder (military data)

RR=2.1 (1.03-3.94)*

**Proportional affected relatives unchanged*

Hoek, et al
Psych Psychiatric Epidemiol
1998; 33:373

Neurodevelopmental Disorders after prenatal exposure to Dutch Famine, 1945



Chinese Famine, 1959-1961

Change in agricultural practice, bad weather

All provinces affected

- Anhui Province - starvation↑ in spring 1959, relieved early 1961
- One psychiatric hospital in region

St. Clair, et al
JAMA 2005; 294:557

Chinese Famine
Rate of Schizophrenia

Year of birth	Adjusted risk	P
1959	0.89 (0.78-1.03)	0.13
1960	2.30 (1.99-2.65)	<0.001
1961	1.93 (1.68-2.23)	<0.001
1962	0.95 (0.87-1.04)	0.28

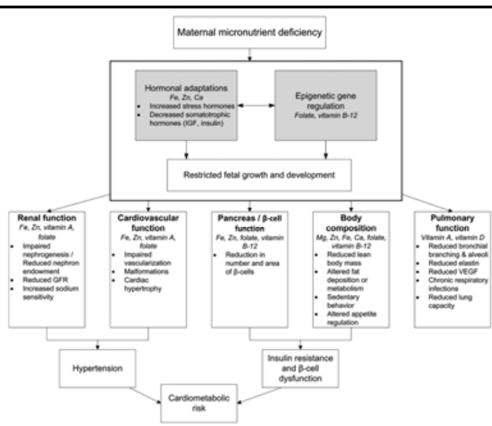
Proportion of familial cases unchanged (17-18%)

St. Clair, et al
JAMA 2005; 294:557

Diet and Other Factors During Famine

Dutch: Ate tulip bulbs
↑Stress (very cold, military control)

Chinese: Ate tree bark, green algae
Weather not harsh,
no military presence



Mechanisms of Folic Acid Effects
Methyl Donor

- Hcys + Methyl* = Methionine;
- Methionine → S-adenosylmethionine
- <u>S-adenosylmethionine</u> is major intracellular methyl donor

* From folate

Mechanisms of Folic Acid Effects

Gene Regulation

- **CpG dinucleotides located in gene regulatory regions:**

  Methylation of the 5' cytosine prevents transcription, turning gene off *

***Imprinting**

Mechanisms of Folic Acid Effects

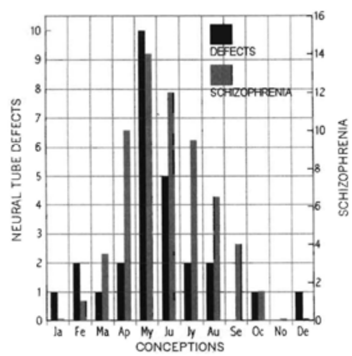
Transmethylation Reactions

- **Methyl groups required for synthesis of AA, proteins, lipids (myelin), etc.**
- **↓ Methyl group availability →**

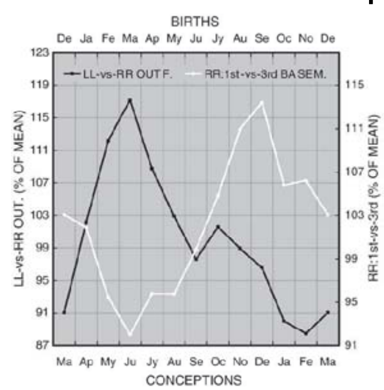
  <u>Slowed tissue growth</u>,

  Inappropriate timing of devel. events

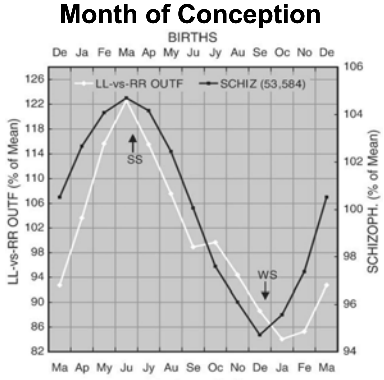
Rate of NTDS and Schizophrenia According to Month of Conception



Handedness vs Month of Conception



Left-Handedness and Schizophrenia vs Month of Conception



Left handedness, schizophrenia, (artistic talent):

Deficit in establishment of lateral asymmetry

Neural Tube Defects:

Failure of neural tube closure

Both occur in early 4th week

- Meta-analysis of 13 data sets (n = 47,866)
- Significant evidence of seasonal anisotropy in handedness

  Left handed people more likely to be born March - July

Jones and Martin
Cortex, 2008; 44:8-12

↑ maternal oxidant stress (intense solar radiation) may interfere with both NT closure and asymmetry development

UV light → ↓ skin glutathione

SUMMARY

- The intrauterine environment exerts a permanent influence on postnatal metabolism and growth
- The mother's fetal life can affect the development of her own offspring
- Influential factors include calories, content of diet, micronutrients, stressors