A Developmental Programming Perspective on Health and Disease Risk

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What determines our health & disease risk?
Worldwide availability and consumption of highly processed, energy dense, low nutritional value foods
Decreased energy expenditure and increased mechanization
What determines our health potential?

Genetics

food → activity → Disease risk
What determines our health & disease risk?

Interactions between early life and postnatal environments

Early life -> Disease Risk
Historical data

"How fast can you make me literate?
— I want to rewrite history."
Hertfordshire, UK, early 1900s
• Chief health inspector and Lady Inspector of Midwives

• Records enabled tracing of 16000 men and women born in Hertfordshire between 1911-1930
Information from one of Miss Burnside’s birth and infant growth records, c1917

<table>
<thead>
<tr>
<th>Weight at Birth</th>
<th>Weight 1st Year</th>
<th>Food</th>
<th>No. of Visits</th>
<th>Condition, and Health Vis</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 1/4 lbs</td>
<td>24 1/2 lbs</td>
<td>B.</td>
<td>11</td>
<td>y</td>
</tr>
<tr>
<td>Healthy &amp; well developed</td>
<td>Buckland School</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 lbs</td>
<td>15 1/4 lbs</td>
<td>B.</td>
<td>12</td>
<td>h. y.</td>
</tr>
<tr>
<td>moved to Bury Green St. Hackam. Had measles, pm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>Boc.</td>
<td>11</td>
<td>y. y.</td>
</tr>
<tr>
<td>T.B. abscess on neck opened. Ant. pitaenelle still open 23 yrs. Abdomen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 1/2</td>
<td>22</td>
<td>B.93</td>
<td>9</td>
<td>y. y.</td>
</tr>
<tr>
<td>Healthy &amp; normal</td>
<td>Buckland School</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Early studies in early life origins of health and disease risk

What is the relationship between chronic disease and birth weight?
Birth weight is associated with chronic disease risk

What did Dr Barker find?

- relationship between birth weight and type 2 diabetes in adult men

Barker & Osmond The Lancet 1(8489): 1077 1986
“Developmental Programming”

The fetal and infant origins of adult disease

_The womb may be more important than the home_

BMJ volume 301, 17 November 1990
Birth weight is a “marker” of the prenatal environment.

*Low birth weight* indicates some adversity (or insult) during the early life environment.
Birth weight poor indicator of growth *pattern*

How is this happening?

The fetal and infant origins of adult disease

*The womb may be more important than the home*

*BMJ* volume 301, 17 November 1990
What could be causing this?
What about nutrition?

1944 - 1945

Only 400 - 800 Calories a day
22,000 people affected by famine and cold.

Among them were pregnant women.
Maternal famine → Children born to these mothers had as adults*:

• Obesity
• Type 2 diabetes
• High blood pressure
• Heart disease

*after controlling for lifestyle and behaviour
Schizophrenia After Prenatal Exposure to the Dutch Hunger Winter of 1944-1945

Ezra S. Susser, MD, Dr PH; Shang P. Lin, PhD

...not just “classic” chronic diseases...
Prenatal Exposure to Famine and Brain Morphology in Schizophrenia

Hilleke E. Hulshoff Pol, Ph.D.
Hans W. Hoek, M.D., Ph.D.
Ezra Susser, M.D., Dr.P.H.
Alan S. Brown, M.D.
Alexandra Dingemans, M.S.
Hugo G. Schnack, Ph.D.
Neeltje E.M. van Haren, M.S.
Lino Moreira Pereira Ramos, M.D.
Christine C. Gispen-de Wied, M.D., Ph.D.
René S. Kahn, M.D., Ph.D.

Objective: The authors assessed the effects of nutritional deficiency during the first trimester of pregnancy on brain morphology in patients with schizophrenia.

Method: Nine schizophrenic patients and nine healthy comparison subjects exposed during the first trimester of gestation to the Dutch Hunger Winter were evaluated with magnetic resonance brain imaging, as were nine schizophrenic patients and nine healthy subjects who were not prenatally exposed to the famine.

Results: Prenatal famine exposure in patients with schizophrenia was associated with decreased intracranial volume. Prenatal Hunger Winter exposure alone was related to an increase in brain abnormalities, predominantly white matter hyperintensities.

Conclusions: Nutritional deficiency during the first trimester of gestation resulted in an increase in clinical brain abnormalities and was associated with aberrant early brain development in patients with schizophrenia. Stunted brain development secondary to factors that affect brain growth during the first trimester of gestation may thus be a potential risk factor for developing schizophrenia.

What are the causes?

Normal Biology
Early life adversity

Changes in biology = Disease

Changes in health expectancy and biological function
Relationships between the developmental and postnatal environment impact on health and disease risk

Developmental Environment

Postnatal Environment

Risk of disease
- diabetes
- heart disease
- Obesity
Developmental Programming:

“Fetal Fortune Telling”

The developing organism uses information (from the mother) to predict its future environment so that it can adapt its development and better its chances of survival.
Predictive Adaptive Responses

The Prediction:
The developing fetus receives information from the mother in the form of hormones, nutrients or oxygen and uses these to predict the environment.

The Adaptation:
The developing fetus will then use this information to adapt its development to better its chances of survival after birth.

These predictions may not be accurate & adaptations not necessary and thus may result in disease.
Can the fetus be “misinformed”? 

**Maternal disease**
- Inflammatory diseases
  - Asthma
  - Periodontal disease

**Pharmaceutical exposures**
- Antidepressants
  - SSRIs

**Drugs**
- Smoking
  - Nicotine
  - THC
- Alcohol intake

Fetal development
The Developmental Origins of Health and Disease

Developmental Environment

Postnatal Environment

Risk of disease

- diabetes
- heart disease
- obesity
- stress/anxiety
Understanding the mechanisms: animal models

Balanced Diet (Control)

Undernourished

High Fat

Mothers’ Diet during pregnancy
Maternal Undernutrition

- Pregnant rats fed 30-50% of control diet
  - decreases birth weight
  - followed by accelerated postnatal growth

Maternal Undernutrition:

- Offspring are obese despite eating control diet!

Body fat %

![Diagram showing body fat percentage comparison between control (CONT) and undernourished (UNP) groups.]
How is this happening?

The “Couch Potato” Syndrome

- Offspring of control mothers
- Offspring of undernourished mothers

**Diagrams:**
- Left: Distance travelled (cm) with Con and UN offspring.
- Right: kcals per g BW with Con and UN offspring.

Accelerated Aging?
Pre- and Postnatal Nutritional Histories Influence Reproductive Maturation and Ovarian Function in the Rat

Deborah M. Sloboda¹*, Graham J. Howie¹, Anthony Pleasants², Peter D. Gluckman¹, Mark H. Vickers¹

¹ The Liggins Institute and the National Research Centre for Growth and Development, The University of Auckland, Auckland, New Zealand, ² AgResearch, Hamilton, New Zealand
What happens to the eggs?
Maternal undernutrition decreased follicle (egg) #’s in offspring ovaries

Primordial follicles decreased

Antral follicles decreased

Bernal et al. PLoS ONE 2010
Maternal undernutrition decreased blood vessel density in offspring ovaries

Chan et al. 2015, Biology of Reproduction
Maternal undernutrition increases oxidative stress levels in offspring ovaries

↑ ovarian oxidative stress

Bernal et al. PLoS ONE 2010
The impacts of prenatal undernutrition

- Fetal Growth Restriction
- Early puberty
- Obesity
- Sarcopenia
- Fatty liver
- Hypertension
- Endothelial dysfunction
- Insulin resistance
- Leptin resistance
- Increased anxiety
- Altered appetite
- Hyperphagia
- Fat preference in diet
- Altered stress hormones
- Increased oxidative stress

Maternal nutrient excess and Maternal obesity
Percent of people that are classified as overweight and obese in Canada in 2009-10

<table>
<thead>
<tr>
<th>Province</th>
<th>Age-standardized prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newfoundland and Labrador</td>
<td>62.3</td>
</tr>
<tr>
<td>Prince Edward Island</td>
<td>55.7</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>57.9</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>61.5</td>
</tr>
<tr>
<td>Quebec</td>
<td>48.0</td>
</tr>
<tr>
<td>Ontario</td>
<td>50.6</td>
</tr>
<tr>
<td>Manitoba</td>
<td>58.3</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>58.1</td>
</tr>
<tr>
<td>Alberta</td>
<td>52.9</td>
</tr>
<tr>
<td>British Columbia</td>
<td>42.9</td>
</tr>
<tr>
<td>Yukon</td>
<td>49.0</td>
</tr>
<tr>
<td>Northwest Territories</td>
<td>56.7</td>
</tr>
<tr>
<td>Nunavut</td>
<td>54.7</td>
</tr>
</tbody>
</table>

http://www.med.uottawa.ca/sim/data/Obesity_e.htm
Maternal obesity and pregnancy....

- Overweight (BMI 25.0–29.9) and obese women (BMI >30) had significantly increased risk for:
  - gestational diabetes
  - preeclampsia
  - cesarean delivery
  - large-for gestational-age infants
Maternal obesity vs excessive pregnancy weight gain

>55% of pregnant women with high pre pregnancy BMI

40% of women gain excessive pregnancy weight

Recommended pregnancy weight gain

Pregnancy Weight Gain vs Pregnancy duration (wks)
Excessive pregnancy weight gain & maternal high fat diet

- Pre-Preg
  - Control: 100% Standard Control diet

- Pregnancy (d0-21)
  - MHF: High-Fat Diet (45%kcal Fat)

- Lactation

Excessive pregnancy weight gain & maternal high fat diet

Maternal Weight Gain

- Control
- Maternal High Fat

Maternal Fat: lean ratio

Connor et al. 2012; J Physiol
Excessive pregnancy weight gain & high fat diet

- offspring of mothers fed a HF diet are born small and end up obese and insulin resistant
- **DESPITE** eating a control diet

Howie et al, J Physiol, 2009
Maternal HF diet accelerates pubertal onset, disrupts reproductive cycles in offspring.

Early puberty

Indicator of ovarian aging

Sloboda et al. 2009 PLoS ONE
Maternal high fat diet results in fetal oocyte loss

Fetal Oocyte #

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>High Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of oocytes (mm$^3$)</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>

* indicates a statistically significant difference between the control and high fat groups.

Tsoulis et al. 2016, Biology of Reproduction
Disparate nutritional diets = similar offspring outcomes

Balanced Diet (Control)

Undernourished

High Fat

Offspring have:

✓ Obesity
✓ Diabetes
✓ Fatty liver
✓ Early puberty
✓ Early reprod aging
Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life

RC Painter,^a^ C Osmond,^b^ P Gluckman,^c^ M Hanson,^d^ DIW Phillips,^b^ TJ Roseboom^a^

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^b^MRC Epidemiology Resource Centre, University of Southampton, Southampton, UK
^c^Liggins Institute, University of Auckland, Auckland, New Zealand
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Transgenerational transmittance of disease risk

Inheritance

Where do we start?

grandmother  mother

YOU!  YOU!
Germ cells determine the next generation
Early life impacts on reproductive development = Transgenerational impacts?

Chan et al. Journal of Endocrinology 2014
Genes carry the information to make proteins
- epigenetics = “on top of” genetics
- genes are turned on and off because of environmental induced changes that occur “on top of” the DNA sequence
  - But NOT in the DNA sequence itself
Epigenetic marks on the DNA control whether genes are “on” or “off”

- DNA methylation
- microRNAs
- Histone changes
Epigenetics during development: a window of vulnerability?

- Epigenetic modifications regulate cell destiny
- Important in primordial germ cells (sperm and oocyte)
Table 1. **IGF2 DMR methylation** among individuals periconceptionally exposed to famine and their unexposed, same-sex siblings

<table>
<thead>
<tr>
<th>IGF2 DMR methylation</th>
<th>Mean methylation fraction (SD)</th>
<th>Relative change exposed</th>
<th>Difference in SDs</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposed (n = 60)</td>
<td>Controls (n = 60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>0.488 (0.047)</td>
<td>0.515 (0.055)</td>
<td>-5.2%</td>
<td>-0.48</td>
</tr>
<tr>
<td>CpG 1</td>
<td>0.436 (0.037)</td>
<td>0.470 (0.041)</td>
<td>-6.9%</td>
<td>-0.78</td>
</tr>
<tr>
<td>CpG 2 and 3</td>
<td>0.451 (0.033)</td>
<td>0.473 (0.055)</td>
<td>-4.7%</td>
<td>-0.41</td>
</tr>
<tr>
<td>CpG 4</td>
<td>0.577 (0.114)</td>
<td>0.591 (0.112)</td>
<td>-2.3%</td>
<td>-0.12</td>
</tr>
<tr>
<td>CpG 5</td>
<td>0.491 (0.061)</td>
<td>0.529 (0.068)</td>
<td>-7.2%</td>
<td>-0.56</td>
</tr>
</tbody>
</table>

*P* values were obtained using a linear mixed model and adjusted for age.

**Persistent epigenetic differences associated with prenatal exposure to famine in humans**

Bastiaan T. Heijmans\(^a,1,2\), Elmar W. Tobi\(^a,2\), Aryeh D. Stein\(^b\), Hein Putter\(^c\), Gerard J. Blauw\(^d\), Ezra S. Susser\(^e,f\), P. Eline Slagboom\(^a\), and L. H. Lumej\(^e,1\)
Are these changes to developmental pathways permanent?
Nutritional Interventions: can we rescue this?

**Methyl Donors**
- Choline
- Folate
  
  *(your mom told you to eat spinach right?)*

**Essential Amino Acids**
- Taurine

**Antioxidants**
- Vitamin C
- Melatonin
Maternal nutrition at conception modulates DNA methylation of human metastable epialleles

Paula Dominguez-Salas¹, Sophie E. Moore¹, Maria S. Baker², Andrew W. Bergen³, Sharon E. Cox¹, Roger A. Dyer⁴, Anthony J. Fulford¹, Yongtao Guan²,³, Eleonora Laritsky², Matt J. Silver¹, Gary E. Swan⁶, Steven H. Zeisel⁷, Sheila M. Innis⁴, Robert A. Waterland²,³, Andrew M. Prentice¹ & Branwen J. Hennig¹
Epigenetics and male reproduction: the consequences of paternal lifestyle on fertility, embryo development, and children lifetime health

Liborio Stuppa, Maria Franzago, Patrizia Ballerini, Valentina Gatta, and Ivana Antonucci
Looking ahead ... 

... Unravelling mechanisms
Long term approach to the early life origins of health and disease risk

Biomedical Sciences

Patients

Public Health

Clinical Studies

Integrated, Capacity-building approach
AKNOWLEDGEMENTS

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