Early life nutrition: the origins of cardiovascular disease?

Caroline HD Fall
MRC Lifecourse Epidemiology Unit
University of Southampton
chdf@mrc.soton.ac.uk

British Nutrition Foundation
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Cardiovascular Disease Mortality
Men and women born in Hertfordshire 1911-1930

SMR

WOMEN
n=5,585
p=0.04

MEN
n=10,141
p=0.005

Birthweight (pounds)
The ‘Barker Hypothesis’

Fetal and early post-natal development is an orchestrated process - everything must happen in sequence and at the right time (‘critical periods’).

It’s moulded by the maternal environment, including nutrition, hormones, toxins, stress.

Many ‘metabolic’ tissues are fixed by birth and deficits can be permanent, and cause disease.
FETAL AND INFANT UNDERNUTRITION

Inadequate ‘building blocks’

Mother can’t mobilise and transport nutrients

Impaired ‘supply line’ womb, placenta, blood flow

Liver
- ↓ Insulin sensitivity

Pancreas
- ↓ Insulin secretion

Muscle, Fat, Bone
- ↓ Muscle
- ↑ Fat
- Insulin resistance

Brain
- Altered appetite centres

Hormones
- ↑ Cortisol

Kidney
- ↓ Nephrons

Blood vessels
- ↓ Elasticity

Heart
- ↓ Muscle

High cholesterol
- Diabetes
- Hypertension

Coronary heart disease
Tyrosine kinase

Tyrosine phosphatase

α

α

β

β

INSULIN

Receptor binding

GLUT 4

Tyrosine kinase

Tyrosine phosphatase

MAP KINASE

ISPK-1

GS PP-1

Glycogen Synthetase

Blood Flow

Transendothelial transport

Receptor binding

GLUT 4

IRS

Blood Flow

Transendothelial transport

Receptor binding

GLUT 4

Tyrosine kinase

Tyrosine phosphatase

MAP KINASE

ISPK-1

GS PP-1

Glycogen Synthetase
Childhood growth of 290 men and women with Type 2 diabetes from a cohort of 8760, Finland

Eriksson JG et al Diabetologia 2003;46:190-194
BMI from birth to adulthood for men and women who developed adult pre-diabetes or diabetes
Type 2 diabetes risk according to birth weight and unhealthy adult lifestyle score

Health Professionals Follow-up Study and Nurses’ Health Study (3 million person years)

Unhealthy lifestyle score
- BMI $\geq 25$
- Current smoker
- Activity $<30$ min/day
- Excess alcohol
- Unhealthy diet

Yanping Li et al. BMJ 2015;351:bmj.h3672
Birthweight and type 2 diabetes

<table>
<thead>
<tr>
<th>Birth Weight (kg)</th>
<th>Odds Ratio for Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2.5</td>
<td>0.8</td>
</tr>
<tr>
<td>3.0</td>
<td>0.5</td>
</tr>
<tr>
<td>3.5</td>
<td>0.4</td>
</tr>
<tr>
<td>4.0</td>
<td>0.3</td>
</tr>
<tr>
<td>4.5</td>
<td>0.2</td>
</tr>
<tr>
<td>5.0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Mysore Parthenon Study
Adiposity (girls)

Age (years)

Subscapular skinfold (mm)

ODM
Control
ODF

* p < 0.05 for the difference between ODM and controls

Krishnaveni GV  *Diabetes Care* 2005; 28: 2919-25 and *Diabetes Care* 2010; 33: 402-4
Mysore Parthenon Study
Fasting insulin (girls)

* p < 0.05 for the difference between ODM and controls

Figure: Fasting insulin levels in girls from the Mysore Parthenon Study. The graph shows the fasting insulin levels (pmol/l) for three groups: ODM, Control, and ODF, across different ages (Birth to 14 years). The * symbol indicates that the difference between ODM and controls is statistically significant at p < 0.05.

References:
Mysore Parthenon Study
Cardiac output during stress test

* p < 0.05 for the difference between ODM and controls

* ODF
* OGDM
* Controls

Krishnaveni GV J Clin Endocrinol Metab 2015; 100:986-93
Other early life exposure associated with later cardio-metabolic outcomes

Maternal exposures

- Pre-eclampsia (high blood pressure and lower cognitive function)
- Smoking (obesity)
- Corticosteroids (high blood pressure, plasma insulin, obesity)
- Stressful events (stress responses)
- Endocrine disrupting chemicals (obesity)

Infant exposures

- Formula v breastfeeding (obesity, diabetes, hypertension, raised cholesterol)
- Early weaning (obesity)
- Stressful events (high blood pressure, altered stress responses)
In rats, maternal protein restriction in pregnancy leads to:

- Raised blood pressure
- Increased adiposity
- Insulin resistance
- Glucose intolerance in the adult offspring
In the mother:
- Energy restriction
- Protein restriction
- Uterine artery ligation
- Glucocorticoid exposure
- High fat diet
- Obesity
- Diabetes

In the adult offspring:
- Hypertension
- Insulin resistance
- Glucose intolerance
- ↑ adiposity
- ↓ muscle mass
Mechanisms of fetal programming

Tissue re-modelling

Nutritional deficit during critical period for nephrogenesis

Reduced nephron number

Increased blood pressure

Accelerated nephron damaged

Renin-angiotensin changes

HYPERTENSION
Epigenetic memory as a mechanism

The brown mouse is genetically identical. Its mother was supplemented with methyl donor nutrients (eg folic acid) which increased DNA methylation, permanently silencing the fetal agouti gene, leading to brown coat colour and absence of adult obesity and diabetes.

The yellow mouse has low DNA methylation around the agouti gene, which gives it the yellow coat and also adult obesity and diabetes.

Waterland RA Mol Cell Biol 2003; 23: 5295-300
A low protein diet (R) in pregnant rats reduces methylation at the glucocorticoid receptor gene in the offspring compared with controls (C). These offspring develop raised adult blood pressure. Adding folate to her diet (9%F) prevents the methylation changes and hypertension.

Lillicrop KA. B J Nutr 2005;135:1382-6
Mechanisms of fetal programming

**Tissue re-modelling**

- Nutritional deficit during critical period for nephrogenesis
  - Reduced nephron number
    - Increased blood pressure
      - Accelerated nephron damaged
        - Renin-angiotensin changes
          - HYPERTENSION

**Plasticity of the epigenome in the periconceptional period**

- Nutritional requirements low but nutritionally sensitive
  - Permanent hypo- or hyper-methylation of key genes eg. GCR
    - HYPERTENSION
‘Primordial’ prevention of adult chronic disease

- No intervention
- Late intervention will help vulnerable individuals
- Early intervention offers potential to for larger effects, improves functional Capacity, and may benefit the next generation

Cardiovascular disease vs. Lifecourse

- Childhood
- Adulthood

Plasticity

Ability to adapt to new challenges
INCAP trial, Guatemala
1969-1977 Cluster randomised by village
Pregnant/lactating women and children <7 years

- **ATOLE**
  - Protein 6.4 g/100ml
  - Energy 900 kcal/l

- **FRESCO**
  - Energy 330 kcal/l

Both supplements contained multiple micronutrients

INCAP trial, Guatemala
Effects on risk factors at 25-42 years. Atole compared with Fresco

<table>
<thead>
<tr>
<th>Conception to 24 months (N=257-332)</th>
<th>Birth to 36 months (N=234-305)</th>
<th>24 to 48 months (N=263-359)</th>
<th>24 to 60 months (N=263-359)</th>
<th>36-72 months (N=198-277)</th>
</tr>
</thead>
</table>

### Measures

- **Fasting Glucose (mg/dl)**
- **Systolic Blood Pressure (mm Hg)**
- **HDL Cholesterol (mg/dl)**
- **Triglycerides (mg/dl)**

Stein AD et al. AM J Epidemiol 2006;164:1160-1170
Long-term health outcomes in offspring of mothers who took part in randomised trials of MMN supplements, started in pregnancy, in LMICs

- 17 MMN trials from a 2015 Cochrane review
- Control mothers received iron and folic acid
- 9 of these trials had follow-up data in the children, aged 6 m to 8 y
- Africa (2), Asia (6), South America (1)

No differences in child mortality (9), WAZ/HAZ (7), blood pressure (3), cognitive function (3) or lung function (1)

- Wrong or inadequate intervention?
- Intervention started too late?
- Insufficient length of follow-up?

*Devkumar D et al. BMC Medicine 2016;14:90*
In animals, induction of maternal under-nutrition limited to a few days peri-conceptionally reduces fetal growth and placental size, and raises blood pressure in the adult offspring.

Mumbai Maternal Nutrition Project
Project SARAS (‘excellent’)

A randomised controlled trial (2006-2012) using green leafy vegetables, fruit and milk to improve women’s diet quality for a sustained period (at least 3 months) before conception and through pregnancy.

The intervention increased birth weight and reduces gestational diabetes.

The children are being studied at 5-8 years (CVD risk markers, body composition, cognition

Potdar R Am J Clin Nutr 2014; 100: 1257-68
Sahariah S J Nutr 2016; 146:1453S-60S
Adolescent girls and boys

- Vitamin B12 alone 2μg/day
- Vitamin B12 + MMN + milk protein
- Standard care

Mechanisms of fetal programming

- Pune Vitamin B12 trial
  - "PRIYA"

Sample collection and storage only

- Metabolome
  - LC-MS
  - 1-carbon metabolites
- Transcriptome
- Methylation
- Genome
- Transcriptome
- Methylation
- HumanOmniExpress
- Illumina 450K array
- Exome Beadchip

Data Analysis Integration Mining

- RCT Nutrient intervention
- DNA
  - RNA
  - Blood
  - Urine
  - Stool
  - Fat
  - Cord blood
  - Buccal smears
  - Placenta

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Summary and messages

• Lower birthweight is associated with increased adult cardiovascular disease and type 2 diabetes

• High birthweight due to maternal diabetes or obesity is associated with increased adult obesity and type 2 diabetes

• Examples of ‘programming’ or permanent metabolic and structural changes causing vulnerability to disease

• Rapid fat gain in childhood and unhealthy adult lifestyles add to the vulnerability

• Possible mechanisms include tissue and endocrine re-modelling, and epigenetic changes

• Trials of peri-conceptional and pregnancy interventions are underway but take time to determine long-term impact

• ‘Primordial’ prevention of CVD is the objective