Early life nutrition and developmental programming of later adult disease

Professor Mark Vickers, Liggins Institute, University of Auckland.
Introduction

- obesity and related metabolic disease have reached epidemic levels

- these have been largely attributed to lifestyle factors such as consumption of high fat and high sugar diets and a decline in physical activity

- what is the relative contribution of early life events to development of obesity and related cardiometabolic disorders?
What determines our health potential?

First 1000 Days + Diet + Activity → Later life disease
The First 1000 Days

- much of a child’s future is determined by the quality of nutrition in the first 1000 days

“..few other aspects of nutrient supply and metabolism are of greater biological importance than the feeding of mothers during pregnancy and lactation”
Altered nutritional exposures during early development can imprint for life

Altered early life exposures during the First 1000 Days can leave an imprint that may have lifelong consequences for the offspring
Critical window of opportunity?

Genotype

Developmental Plasticity

Early life nutrition

Adult Phenotype

Stress, pollution etc.

ENVIRONMENT
First 1000 days

Hanson and Gluckman 2014, Physiology Reviews 94: 1027–1076
Developmental Programming
Definition

“a stimulus or insult operating at a critical or sensitive period of development could result in a long-standing or life-long effect on the structure or function of the organism.”
Margaret Burnside - Lady Inspector of Midwives, 1905-
Records enabled tracing of 16000 men and women born in Hertfordshire between 1911-1930
The Fetal Origins or “Barker” Hypothesis: Early Observations

Mothers, babies and disease in later life, BMJ Publishing Group
Ann Intern Med 2000; 133: p 176-182
- Over 70,000 participants

- Birth weight and mortality from cardiovascular disease are inversely associated in adult women

- Birth weight and risk of non-fatal cardiovascular disease and stroke is also inversely associated in adult women

- Associations not weakened when controlling for childhood socioeconomic group or adjusting for adult lifestyle

Relative risk of non-fatal coronary heart disease and stroke according to birthweight

Rich Edwards et al., BMJ 1997;315:396-400
The Dutch Famine 1944-1945

- the Dutch famine provides a unique “experiment of history” to test the programming hypothesis

- Daily intake reduced from 1800 calories to 400-800 calories

- exposure to maternal malnutrition in early gestation was associated with 2-fold risk of childhood obesity

- 3-fold increase in cardiovascular disease and atherogenic lipid profiles

- 6-fold increased risk for breast cancer
Maternal nutrition – a “U”-shaped curved

Relative risk of development of obesity in the offspring

- Premature leptin surge
- Lack of leptin?
- Maternal hyperleptinemia
- Leptin resistance?

Maternal body weight during pregnancy

Under-nutrition | Normal | Over-nutrition
Maternal Obesity

- Approximately 60% of women of reproductive age (15-44yrs) are either overweight or obese

- leads to increased complications of pregnancy including miscarriage, hypertension, gestational diabetes

- maternal obesity leads to increased risk of obesity and metabolic disease in offspring
Impact of poor early life environment on health in later life

Stress
Hypertension
Obesity
Hepatic Steatosis
Reproductive disorders
Osteoporosis
Hyperlipidemia

Neurodevelopmental disorders
Appetite dysregulation
Allergies, asthma
Type 2 diabetes
Nephron deficit
Sarcopenia

Reduced life span
Not just maternal nutrition!

- increasing evidence for the role of paternal factors in health and well-being of offspring

- Weight loss in males prior to conception can improve health outcomes for the child

- Shared parental responsibility
Transgenerational Effects

Environmental effects  
\[ \downarrow \text{e.g. maternal obesity, stress} \]

- $F_0$ (mother)
- $F_1$ (fetus)
- Germ cells
- $F_2$ generation

The effects of a single environmental exposure can be transmitted transgenerationally. An adverse maternal environment ($F_0$) effects not only the development of the fetus ($F_1$) but can also affect the germ cells which form the $F_2$ generation.

Animal Models

- use of pre-clinical models is essential to understand mechanisms, avenues for intervention strategies and transgenerational effects
Maternal Undernutrition
Moderate maternal undernutrition
- 50% food restriction throughout pregnancy

- Even moderate undernutrition in the rat induces significant obesity, hyperleptinemia and early onset puberty in offspring independent of postnatal diet

Maternal nutrition and insulin resistance and hypertension in adult offspring

"Programming effect"

p<0.05 for effect of maternal diet and postnatal high fat diet

The “Couch Potato” Syndrome

Voluntary Locomotor Activity in Offspring in Adulthood

Activity

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<tr>
<th>Diet</th>
<th>Distance travelled (cm)</th>
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<td>7500 ± 500</td>
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<tr>
<td>Con-HF</td>
<td>7000 ± 500</td>
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<td>UN-Chow</td>
<td>6500 ± 500</td>
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<td>UN-HF</td>
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Food Intake

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<th>Diet</th>
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p<0.05 for effect of maternal diet and post-weaning diet

Maternal Nutrition and Learning

- Maternal undernutrition results in learning differences in offspring in later life.
- This has been replicated in both animal and clinical cohorts.

Landon J et al., Learn. Behav. 2007; 3592:79-86
Effects of Maternal Undernutrition on Offspring

- Blood pressure
- Insulin
- Leptin
- Fat Pad (%)

Food intake
- C-Peptide
- Activity
- R. Temp

* p< 0.05 for maternal diet effect

Reduced lifespan
Maternal Obesity
A maternal obesogenic diet during pregnancy and lactation results in hypertension, insulin resistance and obesity in offspring, *independent* of postnatal diet.

N.B. Obesity can also represent a form of malnutrition due to the potential for nutrient deficiencies.
Maternal Obesity
Offspring of mothers fed a HF diet

- maternal high fat nutrition induces significant obesity in offspring, independent of the level of postnatal diet

Howie et al, J Physiol, 2009
Maternal HF Diet during Pregnancy and Lactation Results in Early Puberty and Obesity in Offspring

Mothers fed a high fat diet throughout pregnancy and lactation. Offspring weaned onto a control diet. Similar effects observed in females.

p<0.0001 for effect of maternal high fat diet
Maternal obesity and inflammation in offspring

- Maternal obesity leads to increased inflammation in livers of offspring at birth

Li, Vickers, Reynolds et al.
Increased maternal sugar intake results in hyperleptinemia in offspring at birth

What determines our health potential?

First 1000 Days + Diet + Activity → Later life disease

Can be “programmed” in the first 1000 days
Programming of taste receptors and appetite

- Maternal obesity can program appetite preferences in offspring
- Also reported in the Dutch Famine cohort with reported preferences for fatty foods

Can programming be prevented via early life nutritional modifications?

First 1000 Days

Rest of Life

Modified from Stefan Johansson, Karolinska Institute Sweden
What interventions?

• Dietary
  • lipids, pre-/probiotics, taurine, vitamins, polyphenols, methyl donors etc...

• Pharmacologic
  • Leptin, growth hormone, insulin sensitizers (GLP-1 analogs etc)

• Behavioral/lifestyle
  • Exercise, counselling, health literacy etc...

When to intervene?

• Pre-conception, pregnancy, lactation, early infancy/childhood, adolescence?
Maternal Taurine Supplementation

Obese mothers

- obese mothers are hyperinsulinemic compared to lean control mothers with increases in inflammatory markers
- these effects are normalised with maternal taurine supplementation

Maternal lipid supplementation

*Conjugated linoleic acid (c9, t11-CLA)*

**Maternal Effects**

- Mothers consuming the high fat diet had significantly impaired insulin sensitivity, which was normalised in HFCLA mothers.

*HF vs CON; +HFCLA vs HF, n=6 litters/group*
Maternal lipid supplementation (CLA)  

Offspring at weaning

- Male and female weanling offspring from obese mothers had impaired insulin sensitivity and increased gut inflammatory markers, which were normalised in offspring of HFCLA mothers

n = 6 litters/group ;*HF vs all other groups
Dietary methyl donors

Folic acid\textsuperscript{1}

Glycine\textsuperscript{2}

Choline\textsuperscript{3}

Mixed supplements\textsuperscript{4}

Maternal supplementation improves metabolic and cardiovascular outcomes in offspring following both undernutrition \textbf{and} maternal obesity

- Maternal choline supplementation reduces low-protein induced elevations in systolic blood pressure and fat mass in adult offspring.
Dietary intervention in obese mothers prior to pregnancy

- dietary intervention in obese mothers 4 weeks prior to conception
- reversed metabolic programming in offspring of obese mothers
- effects persisted into adult life

Zambrano et al., J Physiol, 2010
Transgenerational Effects

The effects of a single environmental exposure can be transmitted transgenerationally. An adverse maternal environment ($F_0$) effects not only the development of the fetus ($F_1$) but can also affect the germ cells which form the $F_2$ generation.

Work in rodents shows programming effects through to the F3 generation.
What about the father?

- Also growing evidence re *paternal* transmission of disease risk
- Obesity increases sperm DNA damage

Chronic high-fat diet in fathers programs β-cell dysfunction in female rat offspring

Ng et al, *Nature*, 2010, 467(7318)
Not “one size fits all”

- Potential that interventions in setting of “intact” systems may lead to adverse outcomes
- How best to identify those “at risk” of programmed disorders? – tailored approach, metabolic biomarkers?
Effects of interventions can be directionally dependent upon maternal nutritional status

Liver 11β-HSD2 expression

Control Control + Leptin UN UN + Leptin

Sex-specific Effects

**MALES**

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Maternal nutrition and the breast milk and infant microbiome

Causal Modelling

- Maternal health (e.g., overweight/obese, GDM)
- Mode of delivery
- Infant sex
- Ethnicity
- Breastfeeding status
- Breastmilk microbiota
- Antibiotic use
- Epigenetic factors
- Growth patterns
- Satiety and immune factors
- Gut microbiome
- Altered risk for overweight/obesity and cardiometabolic disorders
- Transgenerational transmission of disease traits

Moosavi et al., Cell Host Microbe 2019
Breast Milk as a Programming Factor

Human milk is the optimal feeding choice for infants but poor maternal nutrition can impact upon lactation and milk quality:

- Breast milk hormone concentrations are associated with a number of modifiable maternal characteristics\(^1\)

- altered milk composition due to maternal obesity can impact on adipose accumulation in the infant

- breast milk from obese mothers has been shown to have pro-inflammatory properties and decreased neuroprotective factors\(^2\)

- maternal malnutrition can also alter nutritional quality of breast milk and impact on growth and neurological development

- effects can be sex-specific

\(^1\) Chan et al., Int. J Obesity, 2018: 42(1);36-43  \(^2\) Panagos et al., J Perinatology, 2-16: 36(4); 284-90
Practical Guidelines for Positive Action

- Most dietary advice is offered with the aim of avoiding health issues during pregnancy and *minimising risk*

- Need to provide *nutritional guidance* to help optimise the *long term future health of the baby*
To provide a current overview of early life nutrition research

- Provide practical, evidence based recommendations to maximise nutritional status before and during pregnancy, as well as infancy and early childhood, when the foundations of future health are created.
Effective translation of research knowledge

Bench: Basic Biomedical Research

Translational Research (T1) → Bedside: Clinical Research

Translational Research (T2) → Community: Improved Health

Childhood Obesity Epidemic
Discussion

- there is no doubt that alterations in the early life environment can increase the risk for obesity and metabolic disorders in offspring in later life
- the early life period of developmental plasticity i.e. the First 1000 Days, offers an avenue for prevention
- Given the transgenerational impacts, it can also shape a society’s long-term health
Acknowledgments