Altered early life nutrition and programming of later adult disease - A bad start lasts a lifetime

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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 the 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”

www.thousanddays.org
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
Developmental Programming

“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.”
Preconception +

Hanson and Gluckman 2014, Physiology Review 94: 1027–1076
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
Clues from Geography

Hertfordshire, UK, early 1900s

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
American Nurses Study

- 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 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
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

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**Fertility and healthy foetal development, and reducing your child’s risk of diabetes and obesity**

Increased body mass index (BMI) in men, as well as obesity in women, can lessen the chance of the female partner becoming pregnant. Studies have also linked male obesity to problems with embryo and foetal development, and miscarriage.

A mother who is obese when she becomes pregnant is more likely to develop gestational diabetes during pregnancy – increasing the risk of diabetes and weight problems for your child as well.

**PRACTICAL ADVICE**

- If you, or your partner, are overweight, support each other in your efforts to get to a healthy weight, before your baby is conceived.
- Losing 5–10% of body weight increases an overweight woman’s chances of becoming pregnant, and has other important health benefits.
- Women with a BMI of 30kg/m² or more should definitely aim to reduce weight.
- If necessary, talk to your healthcare professional about getting the right balance of nutrients for safe weight loss, as well as appropriate physical activities.

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

Ng et al, Nature, 2010, 467(7318)
The effects of a single environmental exposure can be transmitted transgenerationally. An adverse maternal environment (F₀) effects not only the development of the fetus (F₁) but can also affect the germ cells which form the F₂ 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% of ad-libitum throughout pregnancy

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

Insulin resistance and hypertension in adult offspring

"Programming effect"

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

Maternal Nutrition and Learning

- maternal undernutrition has been shown to lead to learning differences in offspring

- this has been replicated in both animal and clinical cohorts

Landon J et al., Learn. Behav. 2007; 3592:79-86
Programming in offspring following Maternal Undernutrition

**Blood pressure**

<table>
<thead>
<tr>
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<th>UN</th>
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</tr>
<tr>
<td>130</td>
<td>120</td>
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<td>120</td>
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<tr>
<td>110</td>
<td>100</td>
</tr>
<tr>
<td>100</td>
<td>90</td>
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**Insulin**

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<td>10</td>
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<td>5</td>
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**Fat Pad (%)**

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<tr>
<td>4</td>
<td>2</td>
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<td>2</td>
<td>1</td>
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**Intake**

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<td>0.2</td>
<td>0.15</td>
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**C-Peptide**

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<tr>
<td>1000</td>
<td>500</td>
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**Activity**

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<td>4000</td>
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**R. Temp**

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<tr>
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* p< 0.05 for maternal diet effect

Reduced lifespan
Maternal Obesity
Maternal obesity = Offspring obesity

- Maternal high fat nutrition induces significant obesity and early onset of puberty in offspring, independent of the level of postnatal diet – cycle of disease

Howie et al, J Physiol, 2009
Maternal obesity and inflammation in offspring at birth

- 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?

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
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

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
Sex-specific Effects

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
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*
Early life nutrition and the opportunity to influence long-term health: an Australasian perspective.

- 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.