Developmental programming of obesity and related metabolic and cardiovascular disorders

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Introduction

- obesity and related metabolic disorders such as type 2 diabetes have reached epidemic levels
- these increases are largely attributed to lifestyle factors such as poor diet and the decline in physical activity
- now well-established that alterations in early life nutrition can increase risk for obesity and metabolic disorders in offspring

- Can disease “programming” be prevented?
BULK OF THE NATION

1% are underweight
34% are normal weight
37% are overweight
28% are obese

Percentage of males and females who are overweight or obese

69% males
60.6% females
What determines our health potential?

- Food
- Activity
- Disease risk
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.”

You are what mum eats

Health reporter Martin Johnston outlines how a mother’s diet shapes her child’s life.
Predictive Adaptive Response (PARs hypothesis)

in response to “hard times”, the fetus makes a series of metabolic adaptations to survive.

- impaired fetal growth permanently changes the body’s structure and physiology
- adaptive for compromised nutrition
- maladaptive for overnutrition
- impact of nutrition transitions (e.g. rural urban shift and move from traditional diets)
What determines our health potential?

1. Early life
2. Food
3. Activity
4. Disease risk
The Dutch Famine 1944-1945

- A severe famine afflicted the Western part of the Netherlands in the last 6 months of World War II (November 1944 to May 1945)

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

- The Dutch famine provides a unique “experiment of history” to test the ‘programming’ hypothesis
The Dutch Famine 1944-1945

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

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

- 6-fold increase in risk of breast cancer
Relevance to Asian populations

- Rapid increases in rates of obesity and type 2 diabetes in Western Pacific and Asian societies

- Many Asian populations have a higher risk for diabetes and cardiovascular disease at a lower BMI compared to Caucasians
  – different BMI cut-offs
  - E.g. the “thin-fat” Asian-Indian babies, similar BMI but increased abdominal fat

- recent census data – almost 20% of NZ population is now Asian/Pacific Islander

- Effect of nutrition transitions to “Western” diets
Developmental Plasticity
Maternal nutrition – a “U”-shaped curve

Grattan D R Endocrinology 2008;149:5345-5347
Animal models are a key tool for the investigation of mechanisms underlying the early life development of obesity and related metabolic disorders.
Programming of Obesity: Evidence from animal models
Animal models of early life nutritional manipulation

- Control
- Undernutrition
- Supplements e.g. Folic acid
- High fat
- High salt
- Low protein
- High sugar
Animal models of early life nutritional manipulation

Undernutrition

Obesity
Type 2 Diabetes
Heart Disease
Altered appetite
Inflammation
Reproductive Disorders

High fat
High salt
Low protein

High sugar
Maternal Undernutrition

Control UN Mother

Balanced Diet from Birth

Control UN

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

Maternal Obesity

- Over 60% of women of reproductive age (15 to 44 years) in the US are overweight
- Obesity “epidemic” in pregnant women
- Leads to increased complications of pregnancy including miscarriage, hypertension, gestation diabetes

- Maternal obesity leads to increased risk of obesity and metabolic disease in offspring

NHS choices
Mums who eat cake have fat babies

Friday April 4 2008
Maternal Obesity

**Chow** fed 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 Sugar Intake

“...sugar should be thought of, like cigarettes and alcohol, as something that’s killing us”

Robert Lustig, UCSF, 2011
Maternal fructose intake results in increases in obesity-related hormones in offspring at birth

Vickers et al., Endocrinology 2011
- high maternal salt intake resulted in increases in inflammatory markers in maternal fat tissue

Gray, Reynolds, Vickers et al. (unpublished)
Can programming be prevented?
When, why and how?
Role of Leptin

Neonatal Leptin Treatment Reverses Developmental Programming


- All measured metabolic consequences of maternal undernutrition were reversed by a period of neonatal leptin treatment
- The effects were permanent and specific to offspring of maternally undernourished offspring
  - has been repeated in other models/species
  - of note, leptin is present in breast milk but not infant formula
Maternal Taurine Supplementation

Obese mothers

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

Vickers, Li et al (unpublished)
Physical activity

UN offspring respond well to moderate exercise

Miles JL et al., Endocrinology 2008
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
Epigenetics
- heritable changes in gene function that do not alter DNA sequence

Methyl Donors

Folic acid\(^1\)

Glycine\(^2\)

Choline\(^3\)

Maternal supplementation improves metabolic and cardiovascular outcomes in offspring

- interventions in setting of “intact” systems may lead to adverse outcomes
- how best to identify those “at risk” of programmed disorders? — tailored approach, metabolic markers
- 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 offers an avenue for prevention
Discussion

- Obesity begets obesity so a vicious cycle ensues
- Transgenerational “programming”