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 ?***

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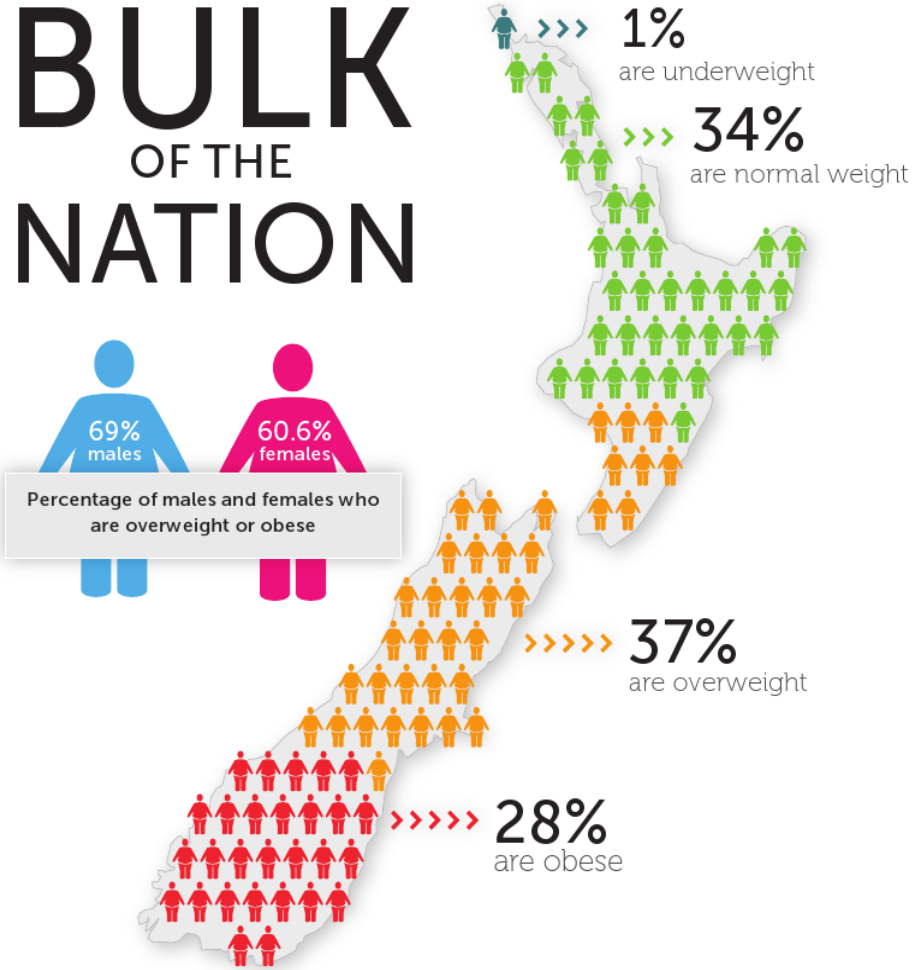
BULK OF THE NATION



Fat NZ

We're second-heaviest among 50 countries

Experts warn health crisis is looming

Martin Johnston health
martin.johnston@nzherald.co.nz

New Zealand adults are on average the second heaviest among 50 countries, a beast list reveals — prompting warnings of a looming medical crisis for some Kiwis.

The average Kiwi was estimated to weigh 81.3kg last year, lighter only than the average American, who weighed 82.7kg.

The weight list was compiled by the Bloomberg news service using data from the World Health Organisation, the OECD and a survey funded by the US Agency for International Development.

It does not include any Pacific countries, where rates of obesity are up to more than twice those of many Western nations.

In separate statistics, Bloomberg recorded New Zealand women as the sixth heaviest in the world at an average 74.6kg, and Kiwi men as 8th heaviest at 88.6kg.

Despite the Pacific gap, the list has retrigered alarm bells at some public health experts about New Zealand's increasing rate of obesity. It has also surprised Maori Party co-leader Tariana Turia, who has had a struggle with her weight.

Bloomberg rankings

The rankings are skewed by the obesity rate in Pacific Island nations, 79 per cent of adults are obese, says the World Health Organisation data. The adult obesity rate in Kiribati is 51 per cent, in French Polynesia, 41 per cent and in American Samoa, 75 per cent. The US rate, measured in 2006, was 34 per cent. The latest New Zealand rate, in the 2011/12 health survey, was 28 per cent.

"I have travelled and seen obesity worldwide ... I wouldn't have thought [New Zealand] would be second in the world," said Mrs Turia, who lost 35kg after she paid to have obesity surgery in 2009.

Obesity increases a person's risk of developing type 2 diabetes, high blood pressure and heart disease.

Professor Don Matheson, of the Centre for Public Health Research at Massey University and a former ministry of health chief, said Kiwi gymnasts were becoming overwhelmed by type 2 diabetes and its complications, such as kidney failure.

New Zealand was heading for the same sort of crisis "for some populations", he said.

Ethnic groups in New Zealand have widely differing rates of obesity. The Pacific group has the highest rate, 68 per cent of adults. Maori are at 46 per cent, Europeans and "others" 26 per cent and Asian 16 per cent.

The obesity rate is also much higher (40 per cent) among people living in the most deprived areas than among people in the least deprived localities (23 per cent).

Otago University senior research fellow Dr Rachael McLean said having to deal with the complications of type 2 diabetes, such as limb amputations, blindness and renal dialysis, had "huge consequences" for the health system.

She urged the Government to adopt community and school-based activity and nutrition schemes.

The Government focus for new initiatives on businesses is on mothers and babies.

It is also spending more than $10 million extra in the coming financial year on more screening for diabetes and cardiovascular disease, and on providing more "green prescriptions", in which GPs and nurses encourage patients to get more exercise and improve their diet.

Average adult weight estimates, 2012

1. United States 82.7 kg
2. New Zealand 81.3
3. Australia 81.1
4. Czech Republic 81
5. United Arab Emirates 80.83
6. Slovakia 80.82
7. Norway 80.6
8. Canada 79.8
9. Germany 79.71
10. Hungary 79.68
11. United Kingdom 79.3
50. Ukraine 72

How the data was compiled

Weights were calculated by adapting the standard Body Mass Index (BMI) formula: BMI = (703 x kg) / (m x m). Data came from the World Health Organisation's weight-height data cases from OECD Society at a Glance report and a survey project funded by the US Agency for International Development. Trend lines, 2012 BMI, statistics a linear trend since adapted to statistics from 1980 to 2006.

Source: Bloomberg / Picture: Getty Images / Herald graphic

What determines our health potential?

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.

Audiences shunned Professor David Barker when he first suggested that the answers to some of the West's worst diseases lay in the womb. "People used to walk out of the room," he says.

Now they queue to hear the head of the British Medical Research Council's epidemiology unit speaking about his theory that what happens before birth can set people up for heart disease, diabetes and stroke in later life.

Professor Barker says the key problem is a nutritional mismatch: shortages in the womb, followed by surpluses in childhood and adulthood.

Heart disease remains the leading killer of New Zealanders, accounting for nearly 30 per cent of deaths, despite a big reduction since 1970. And the incidence of diabetes is soaring as the country's waistline expands.

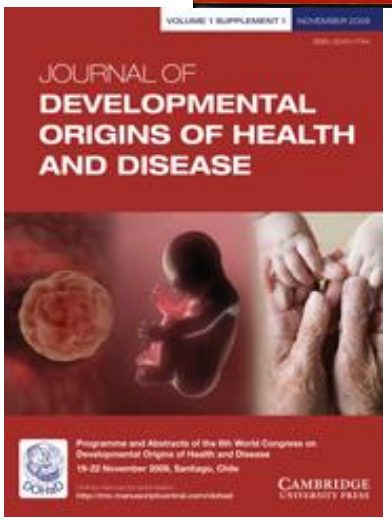
Professor Barker says adult lifestyle, the target of healthy-heart campaigners, provides some of the answers to heart disease. But it could not explain why one person who gulped cream and smoked lived to 95, while another who obeyed the health messages on diet, exercise and smoking died at 40.

"To say it's genetic is to dismiss it. The reality is that it's about how the

HARD-WIRED: Nutrition in the womb influences all of life. PICTURE / FOTOPRESS

"The human baby is very plastic . . . it responds to the mother, it's shaped by the mother."

Professor David Barker



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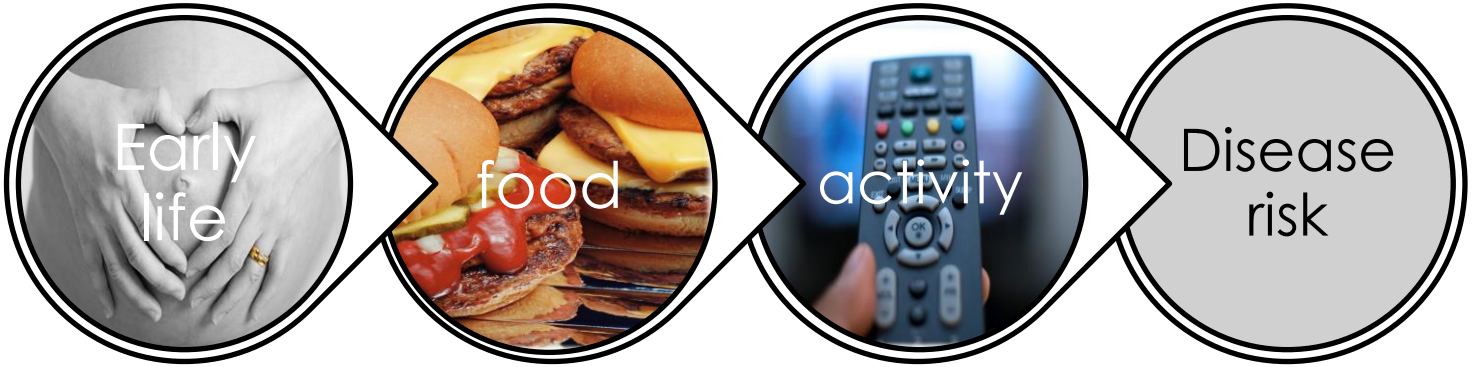
Predictive Adaptive Response (PARs hypothesis)

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?



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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

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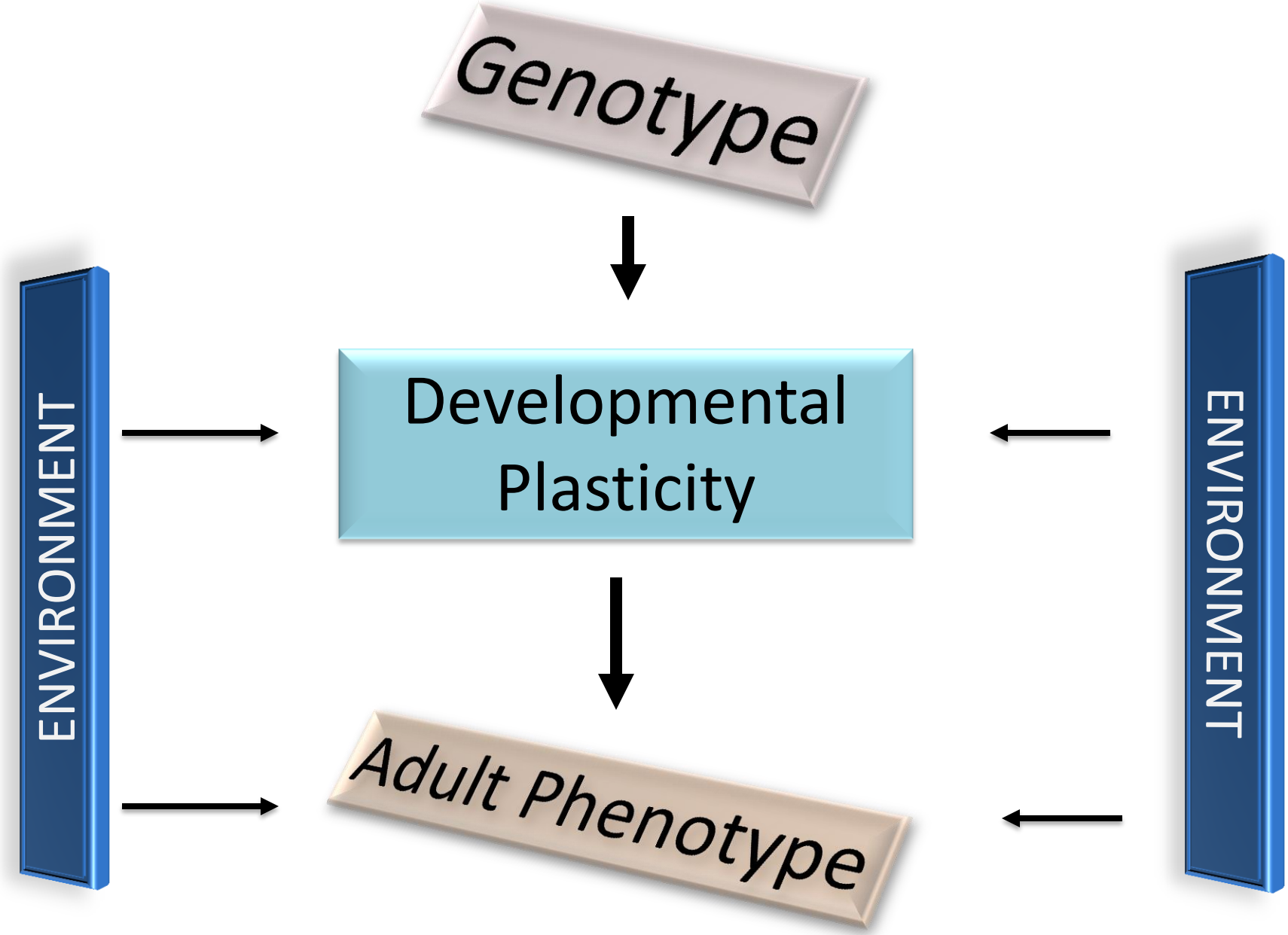

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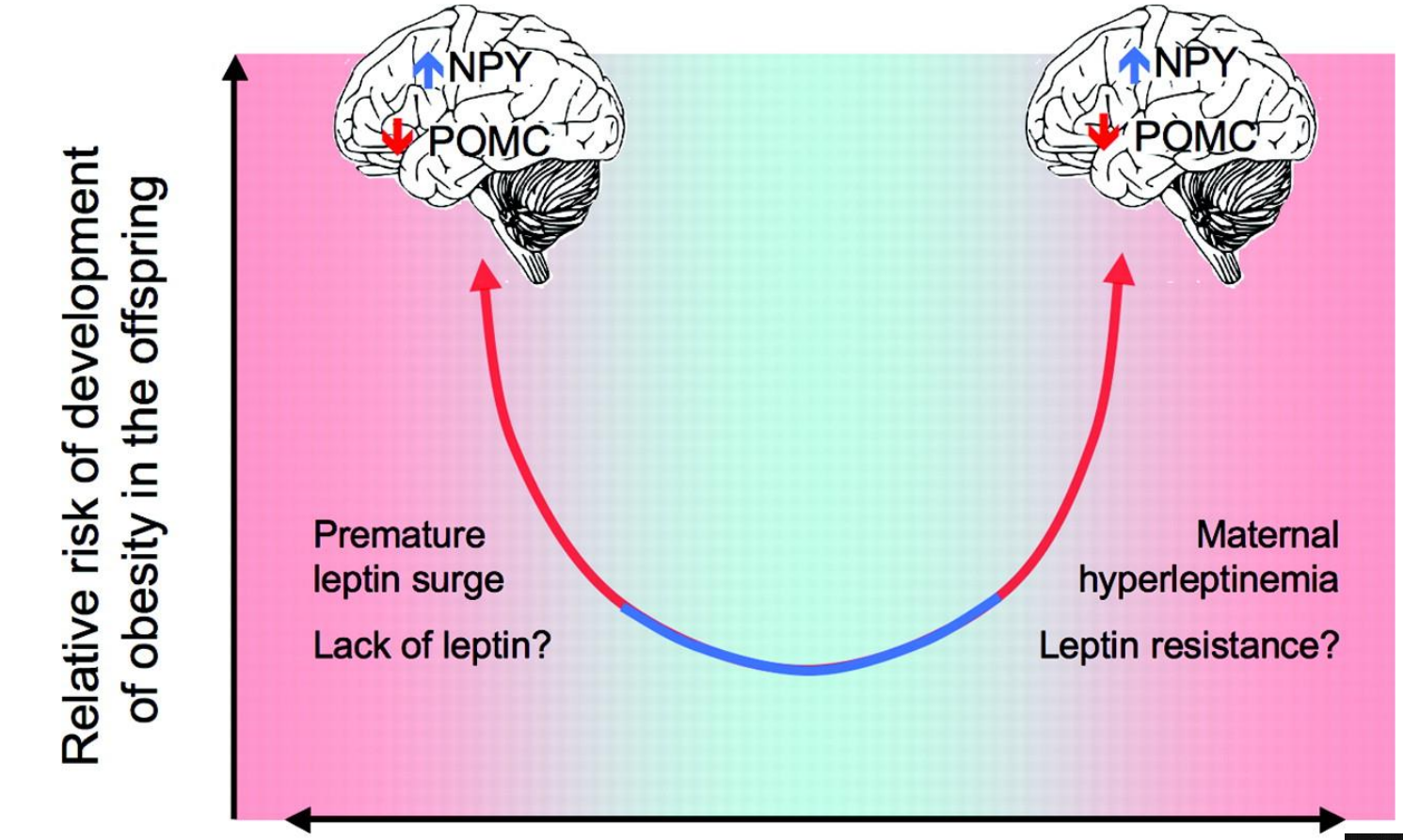
Maternal nutrition – a "U"-shaped curved



Grattan D R Endocrinology 2008;149:5345-5347

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Animal models are a key tool for the investigation of mechanisms underlying the early life development of obesity and related metabolic disorders

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Programming of Obesity:
Evidence from animal models

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Animal models of early life nutritional manipulation

Control

High fat

Undernutrition

High salt

Supplements
e.g. Folic acid

Low protein

High sugar

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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

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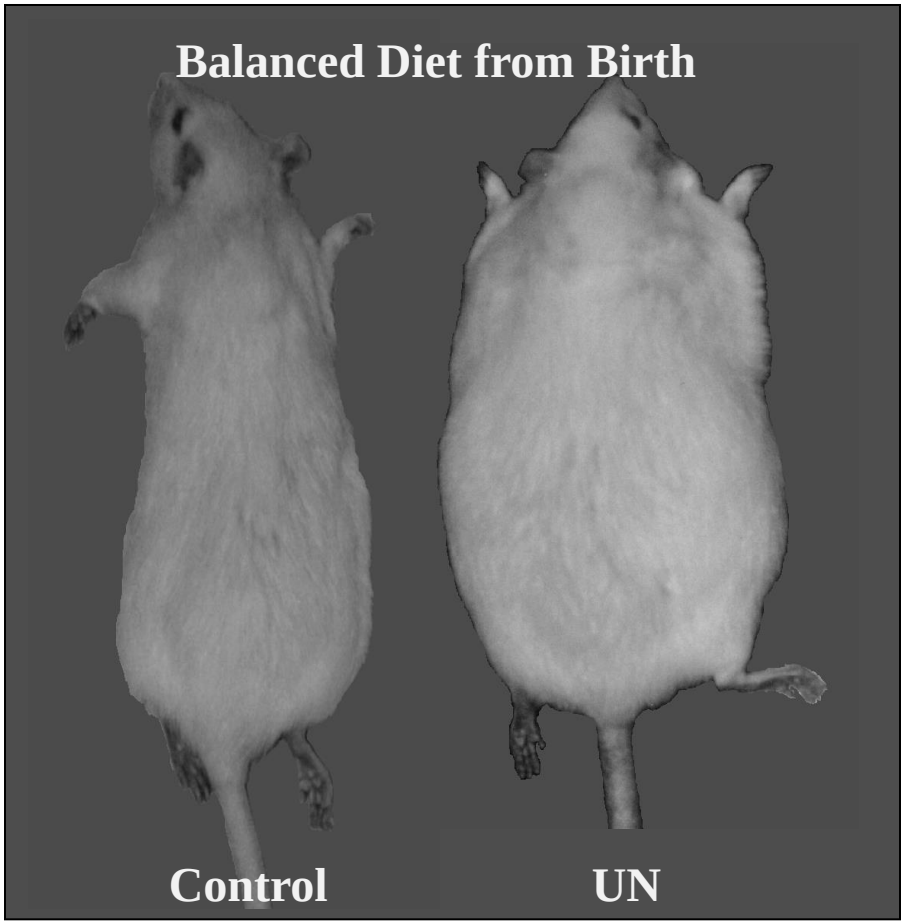
Maternal Undernutrition

Control UN Mother



Vickers et al, Am J Physiol. 2000

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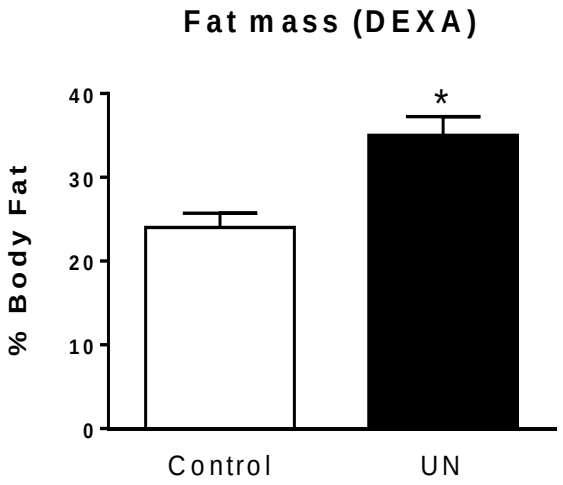
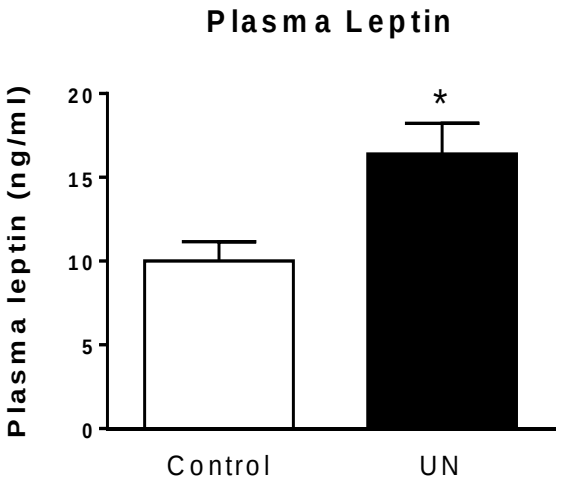
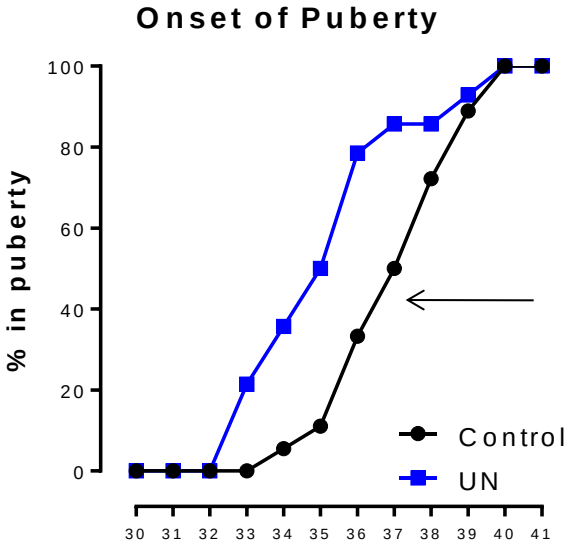
Moderate maternal undernutrition

- 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

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Howie & Vickers et al, Br J Nutrition, 2012

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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

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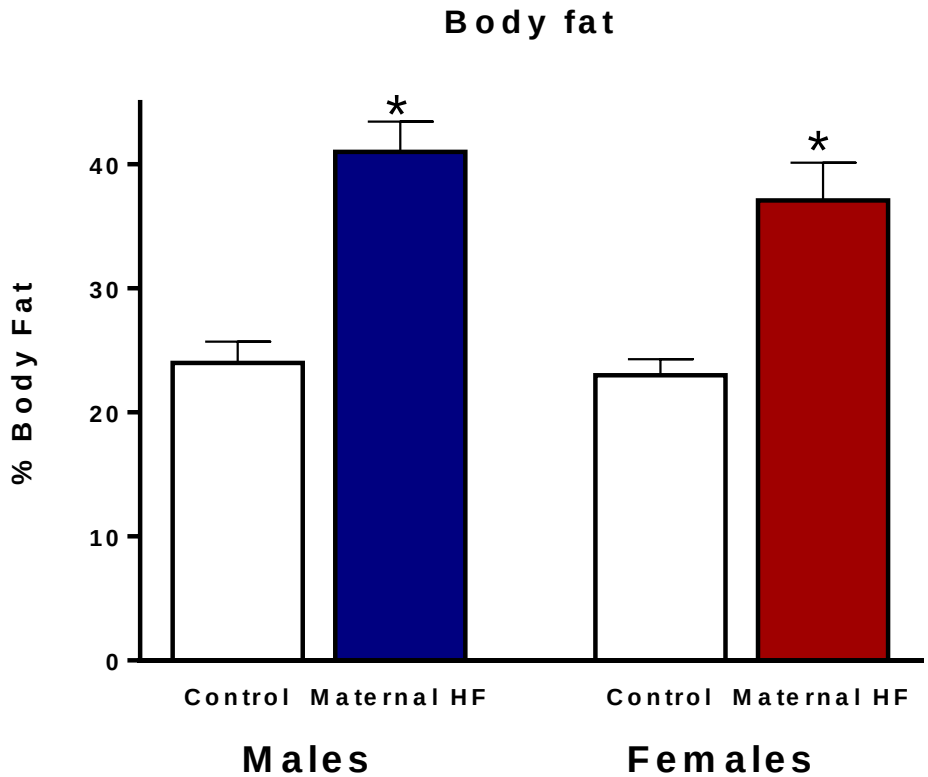
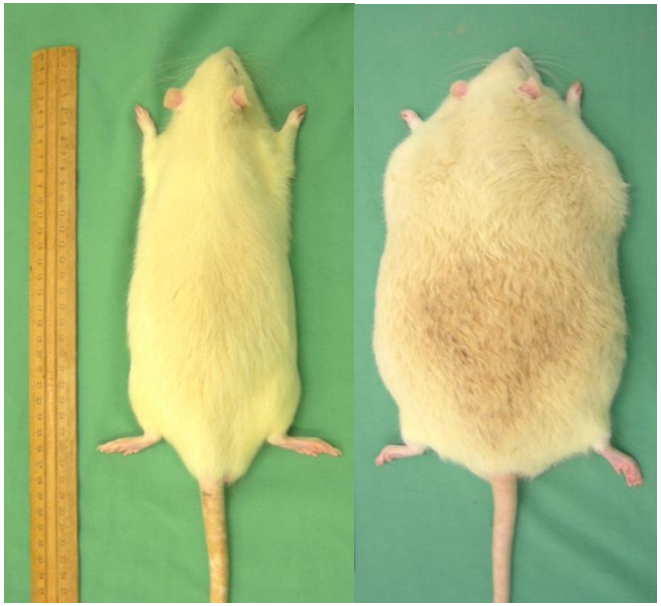
Maternal Obesity

<u>Chow</u> fed offspring of mothers fed a HF diet





Control MHF

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

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Howie et al, J Physiol, 2009

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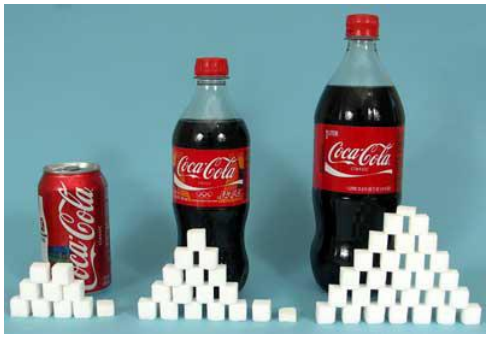
Maternal Sugar Intake

"..sugar should be thought of, like cigarettes and alcohol, as something that's killing us"

Robert Lustig, UCSF, 2011



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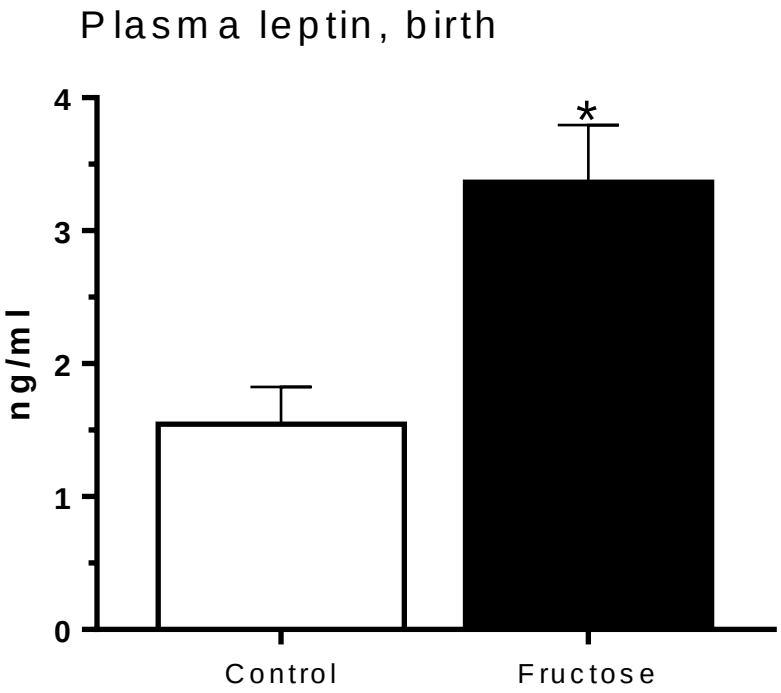
Maternal Fructose Intake



Maternal fructose intake results in increases in obesity-related hormones **in offspring at birth**

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Vickers et al., Endocrinology 2011

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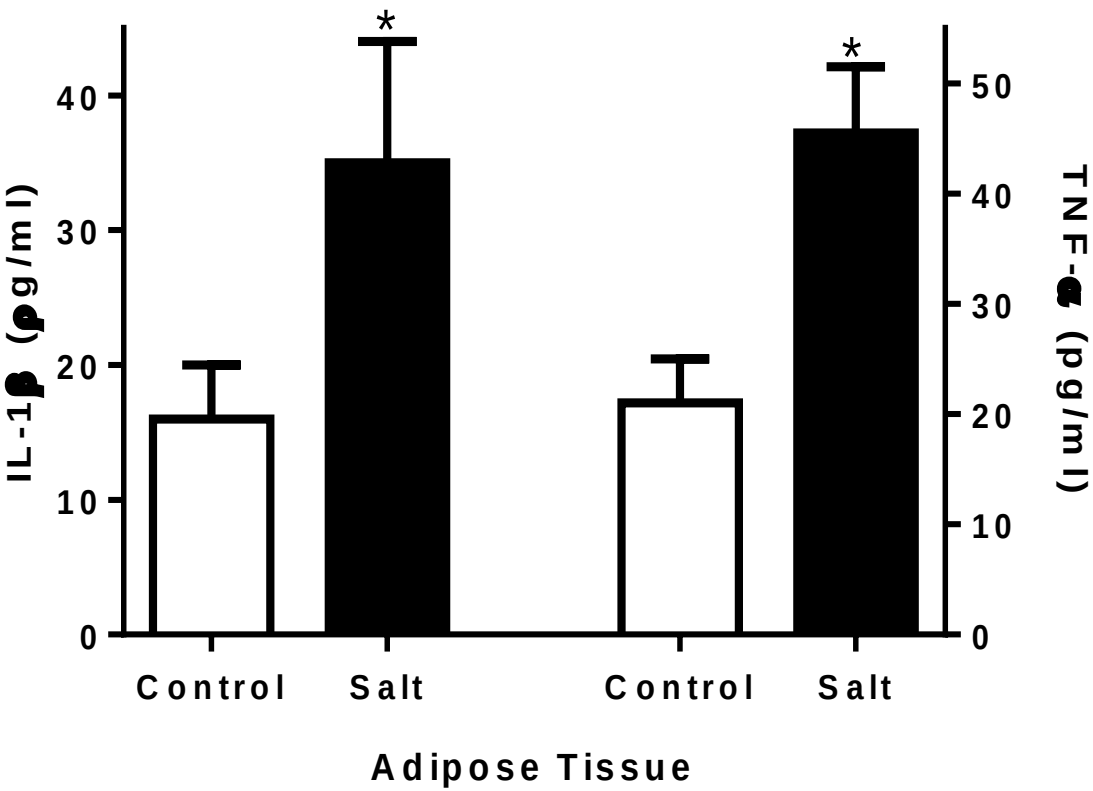
Maternal Salt Intake



- high maternal salt intake resulted in increases in inflammatory markers in maternal fat tissue

Gray, Reynolds, Vickers *et al.* (unpublished)

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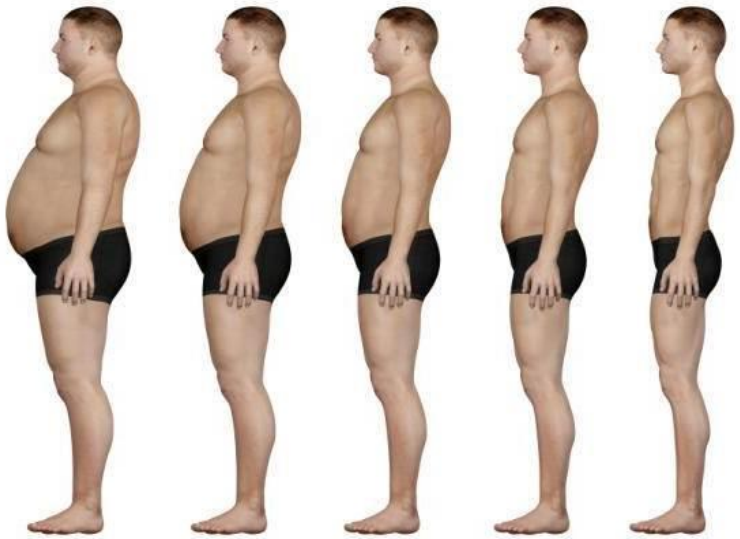
Can programming be prevented ?



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CRITICAL WINDOWS OF DEVELOPMENT

When, why and how ?

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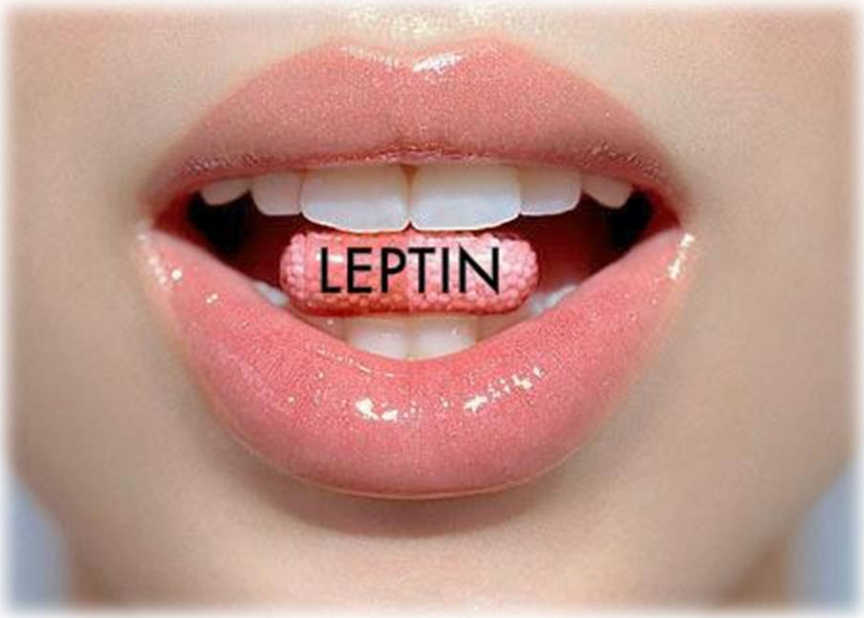

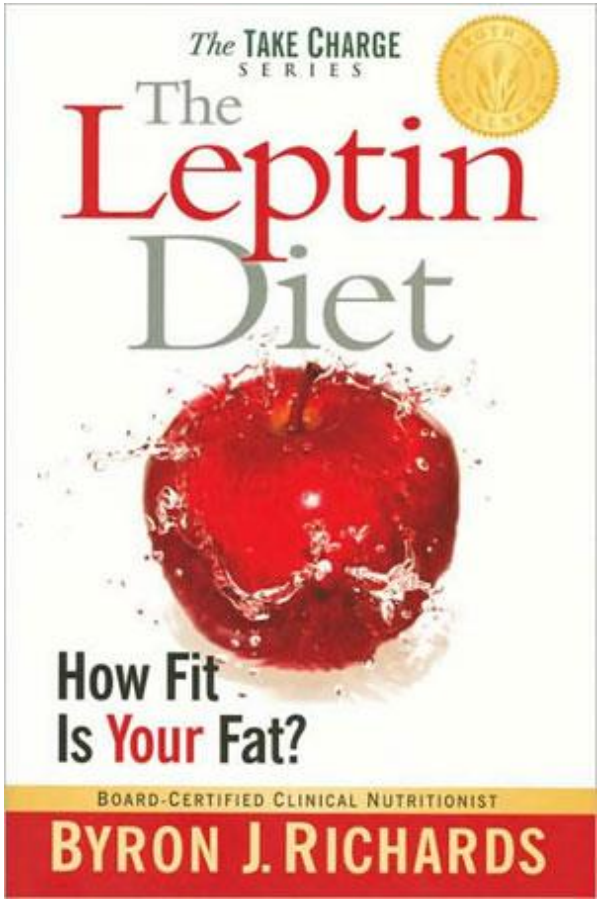

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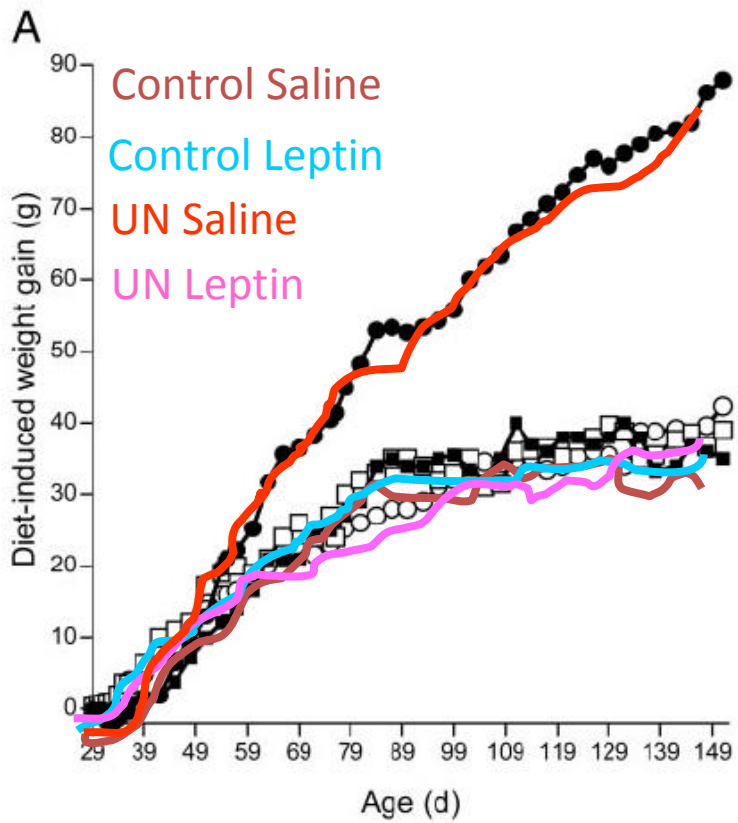
Role of Leptin

Neonatal Leptin Treatment Reverses Developmental Programming

Endocrinology 146(10):4211–4216

doi: 10.1210/en.2005-0581

M. H. Vickers, P. D. Gluckman, A. H. Coveny, P. L. Hofman, W. S. Cutfield, A. Gertler, B. H. Breier, and M. Harris



- 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*

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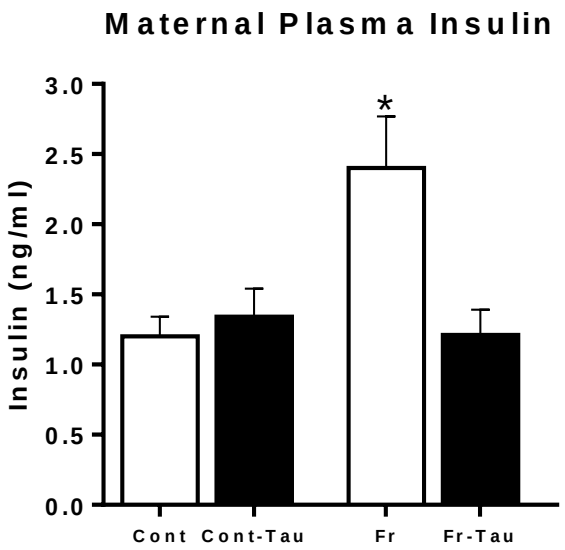
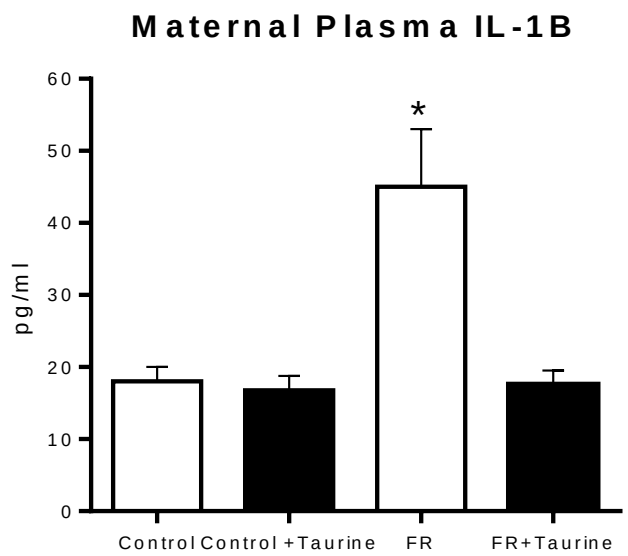
Maternal Taurine Supplementation

Obese mothers





- fructose supplemented mothers are hyperinsulinemic compared to control mothers with increases in inflammatory markers

- these effects are normalised with maternal taurine supplementation

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Vickers, Li et al (unpublished)

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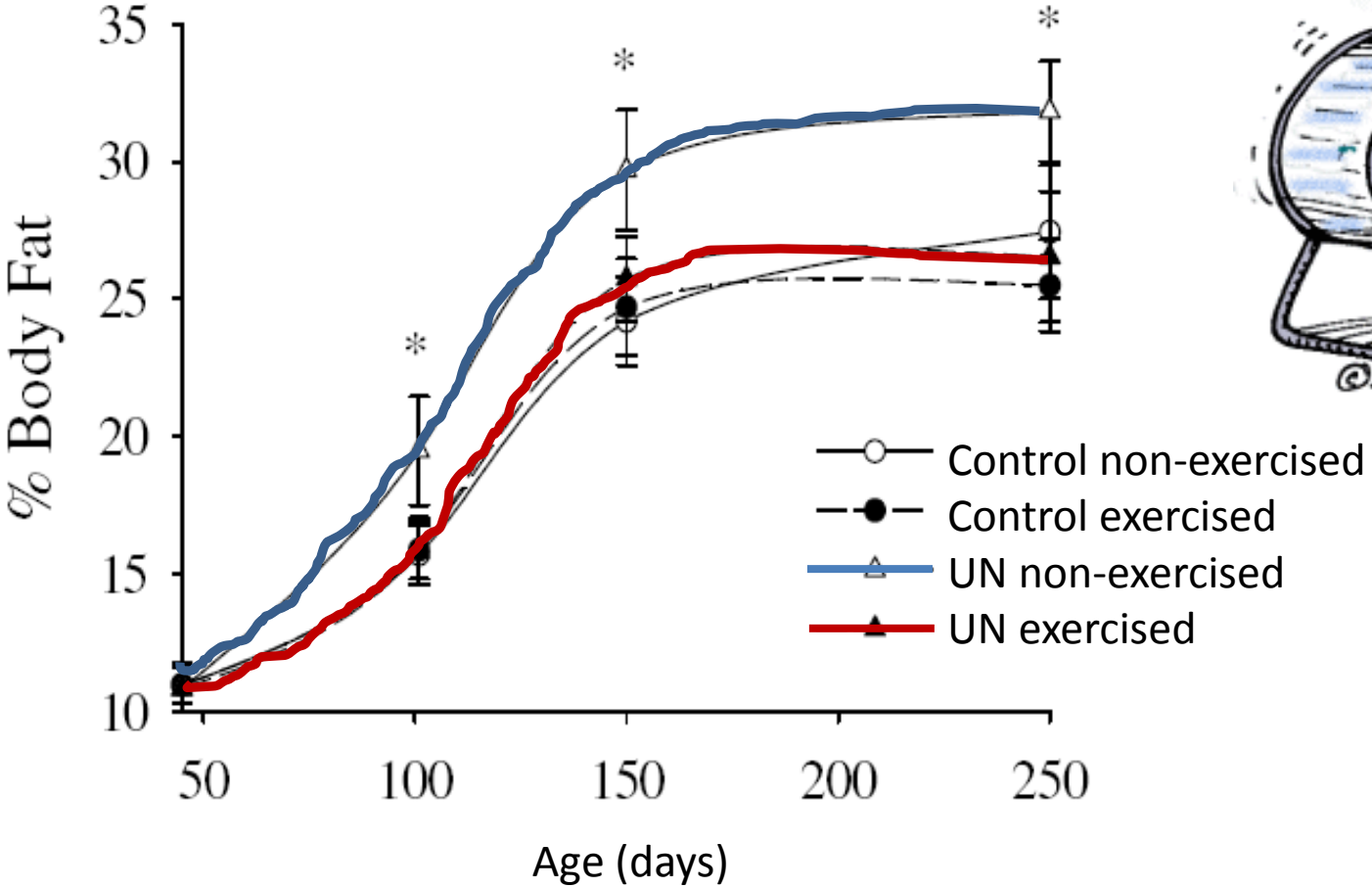
Physical activity



UN offspring respond well to moderate exercise

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Miles JL *et al.*, Endocrinology 2008

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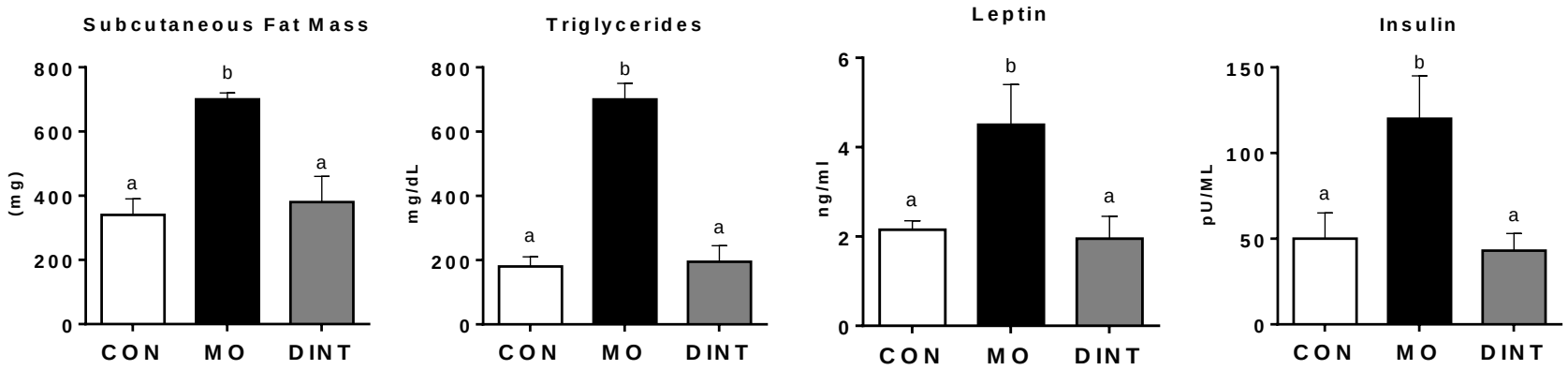
Dietary intervention in obese mothers *prior* to pregnancy



- 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

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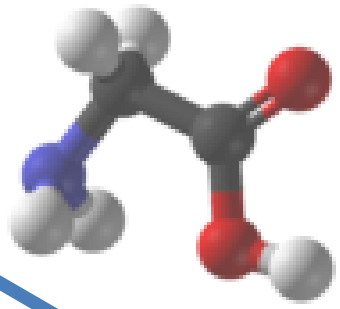
Epigenetics

- 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

1. Torrens et al, (2006)
2. Jackson et al, (2002)
3. Vickers et al, (2012)

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- 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

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 offers an avenue for ***prevention***

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Discussion

- Obesity begets obesity so a vicious cycle ensues

- Transgenerational “programming”

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