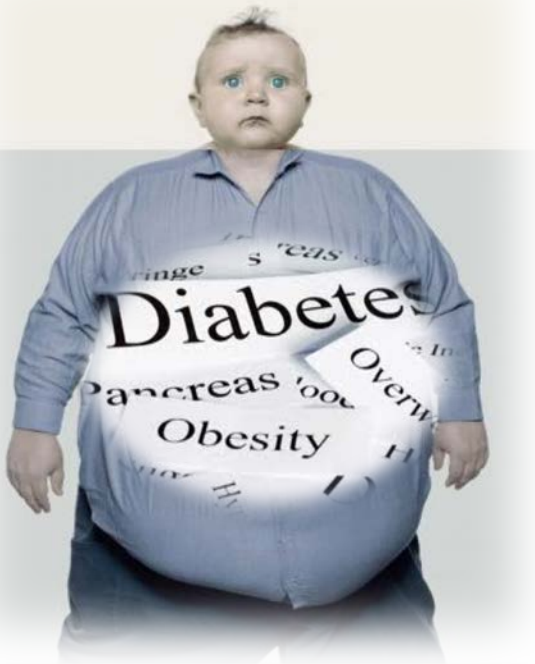
Altered early life nutrition and programming of later adult disease
- A bad start lasts a lifetime



First 1000 days of life

9th April 2019

Professor Mark Vickers,
Liggins Institute, University of Auckland

Gravida
HEALTHY START WORKFORCE PROJECT
A healthy start to life starts with all of us
Māu, māku, mā tātou e ora ai

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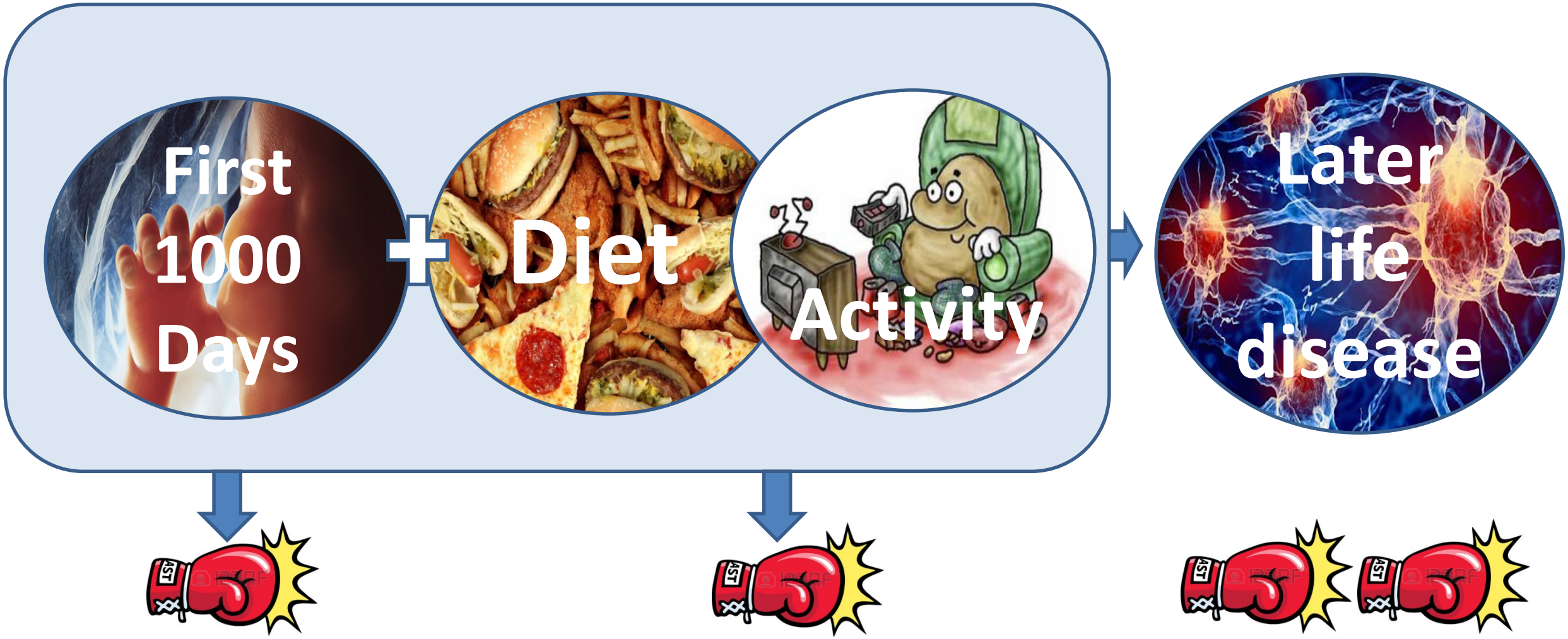
Introduction

- 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

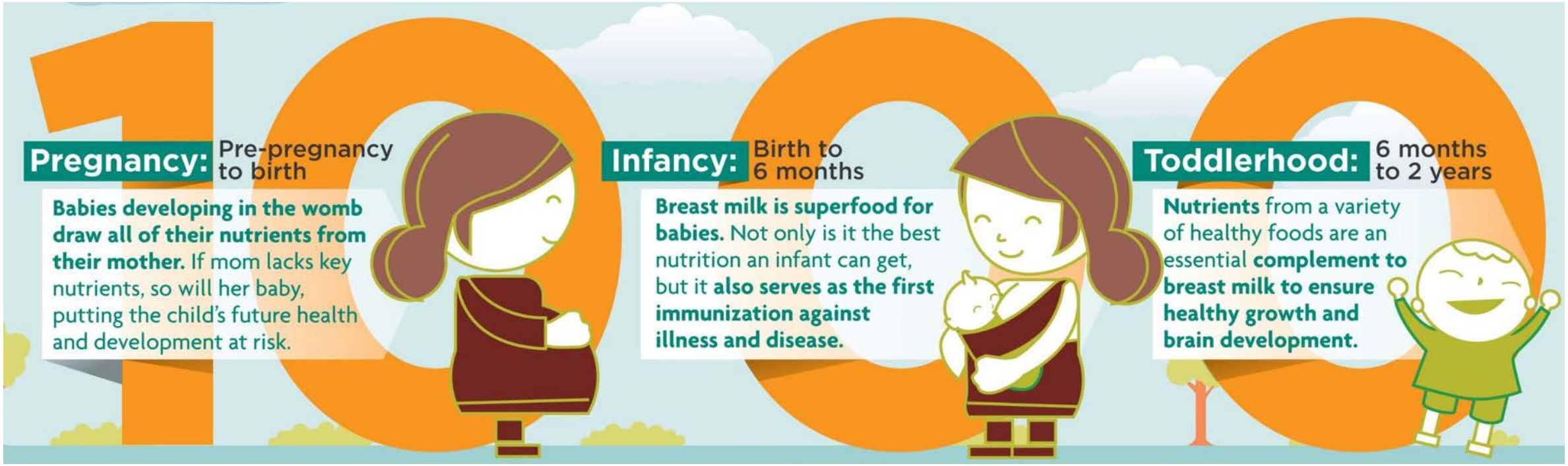
- *what is the relative contribution of early life events to development of obesity and related cardiometabolic disorders ?*

What determines our health potential?



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

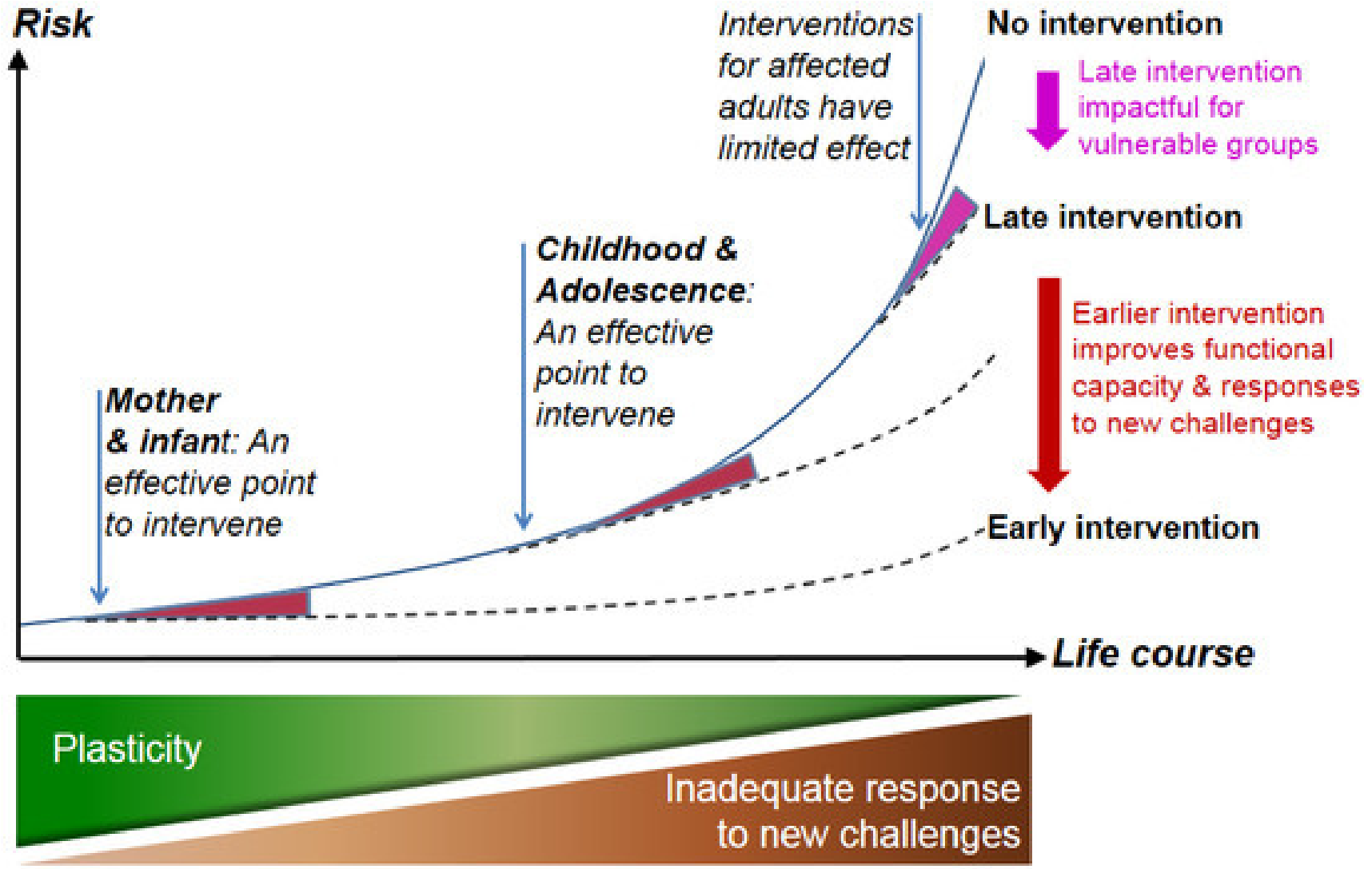
Altered nutritional exposures during early development can imprint for life

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

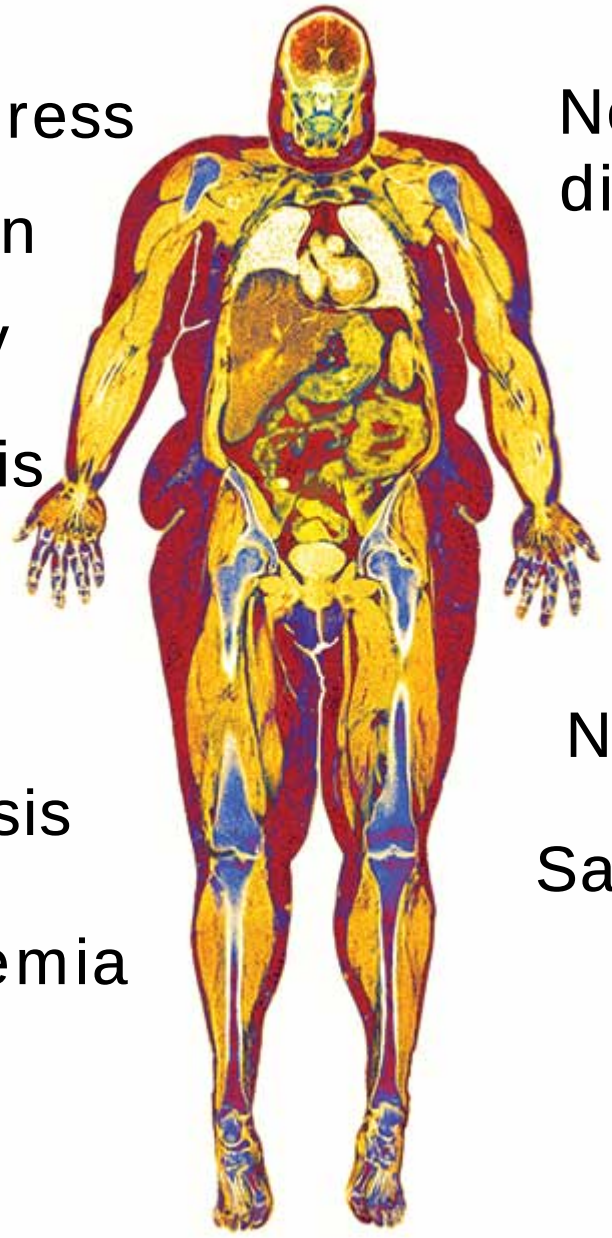
Obesity

Hepatic Steatosis

Reproductive disorders

Osteoporosis

Hyperlipidemia



Neurodevelopmental disorders

Appetite dysregulation

Allergies, asthma

Type 2 diabetes

Nephron deficit

Sarcopenia

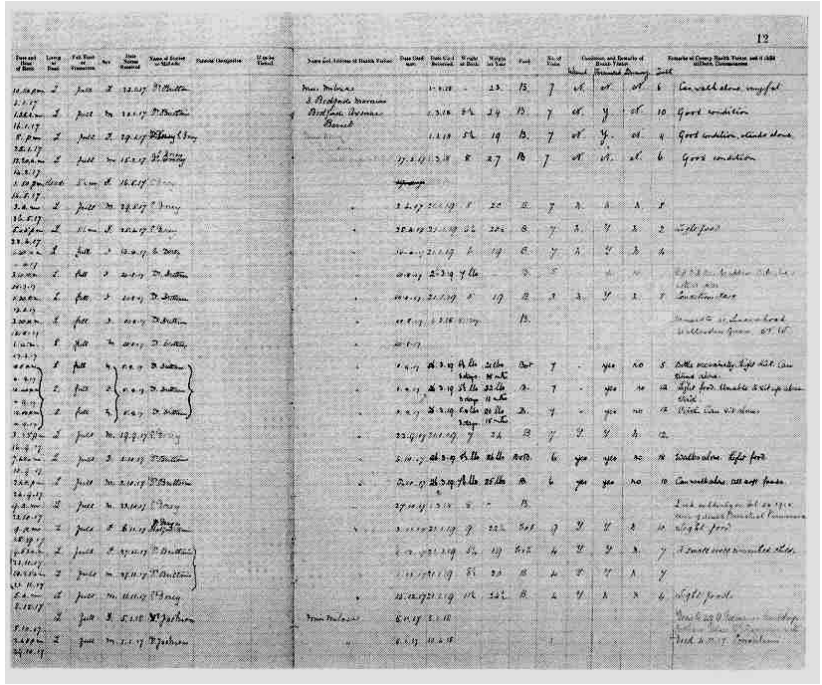
Reduced life span

Clues from Geography

FIG 3.1—*Mothers in Hitchin, Hertfordshire at the turn of the century.*

Hertfordshire, UK, early 1900s

FIG 3.3—*Ethel Margaret Burnside aged 17 years.*



Margaret Burnside -Lady Inspector of Midwives, 1905-

Records enabled tracing of 16000 men and women born in Hertfordshire between 1911-1930

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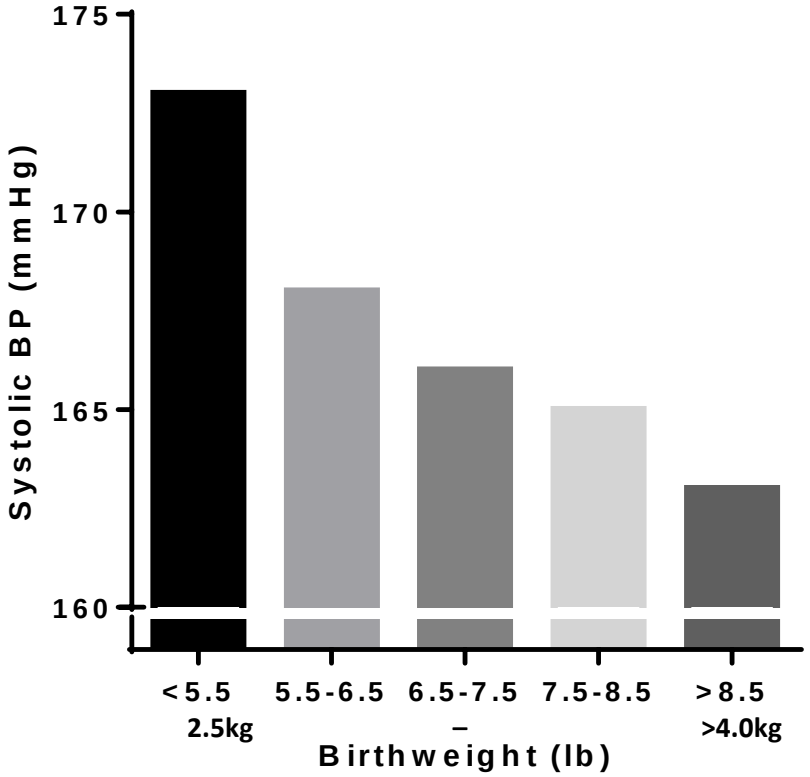
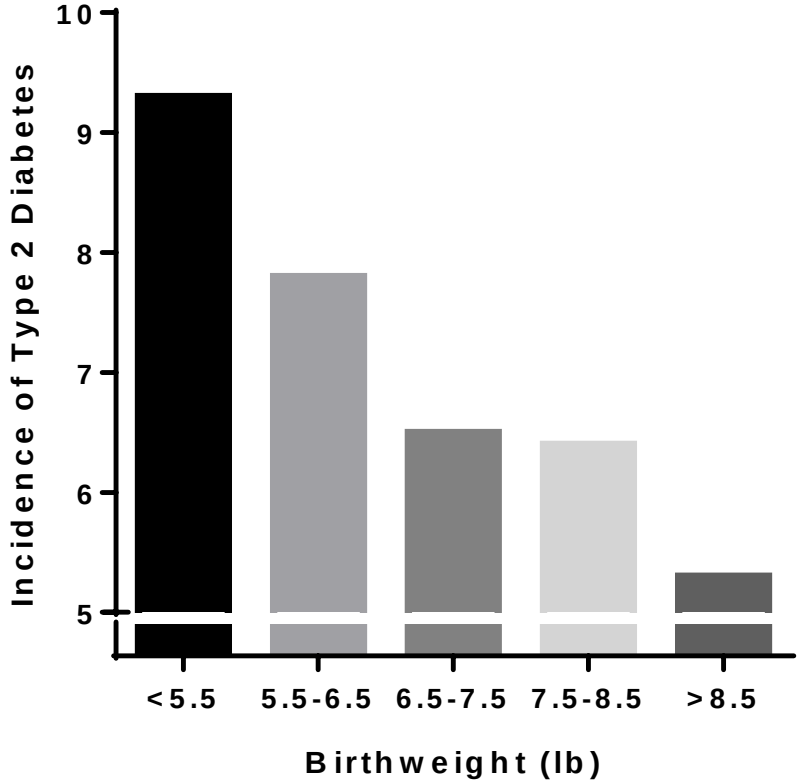
The Fetal Origins or "Barker" Hypothesis: Early Observations





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

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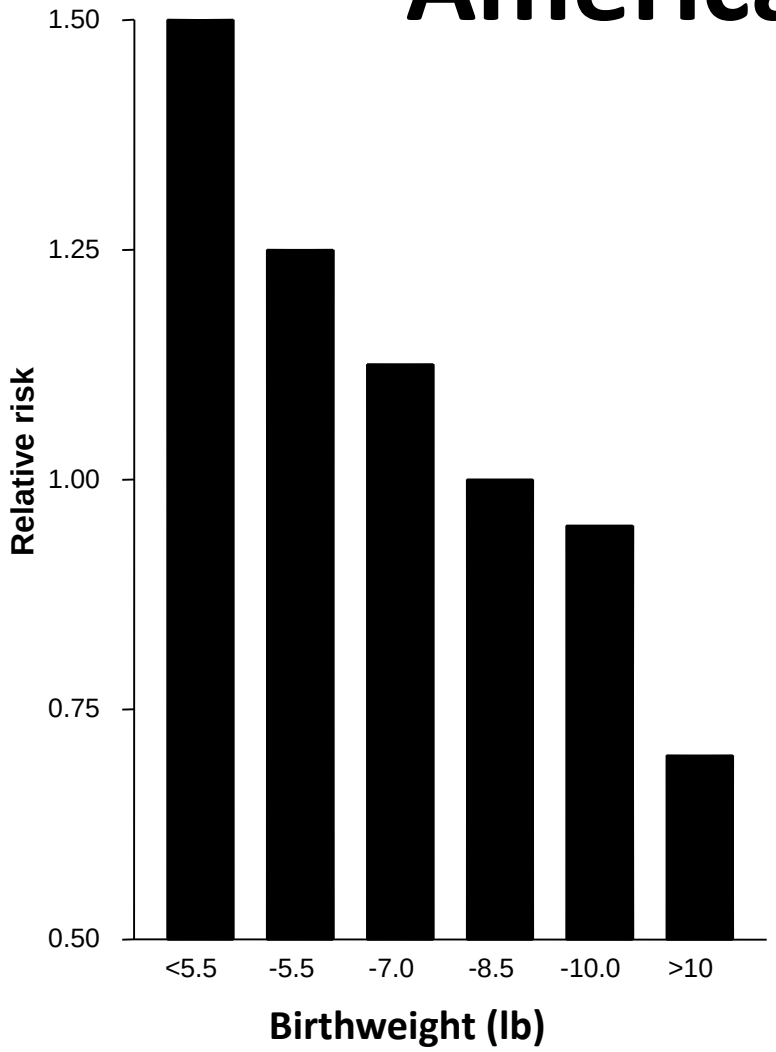
American Nurses Study



-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

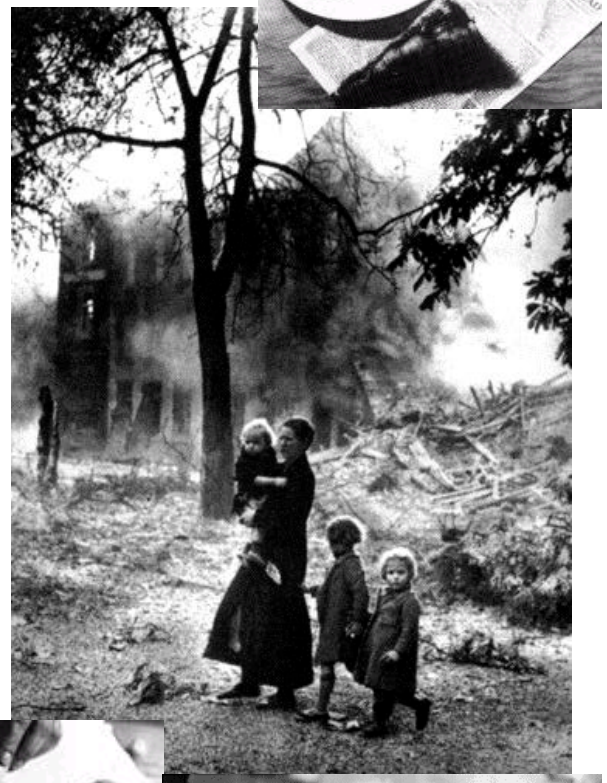
- the Dutch famine provides a unique “experiment of history” to test the programming hypothesis

- 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

2. PRE-CONCEPTION

LOSE EXCESS WEIGHT
(men and women)

A FOUNDATION FOR

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.

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

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

Ng et al, Nature , 2010, 467(7318)

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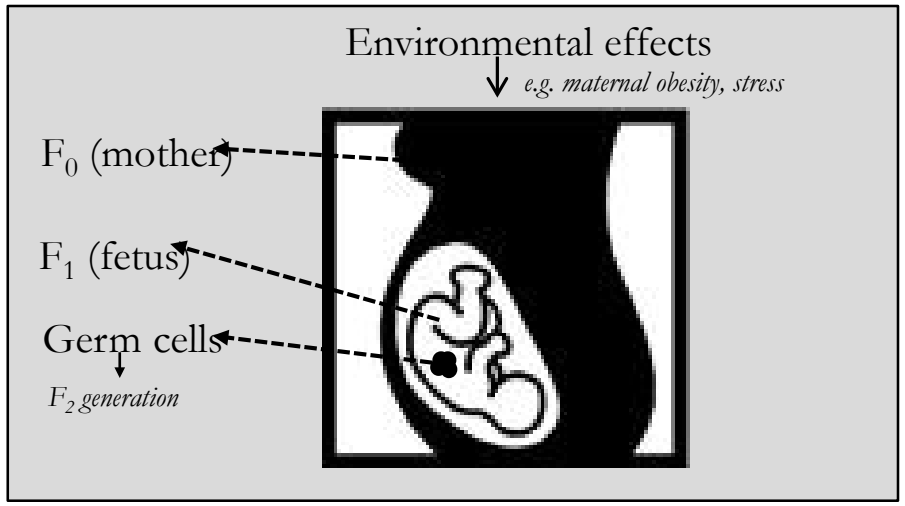
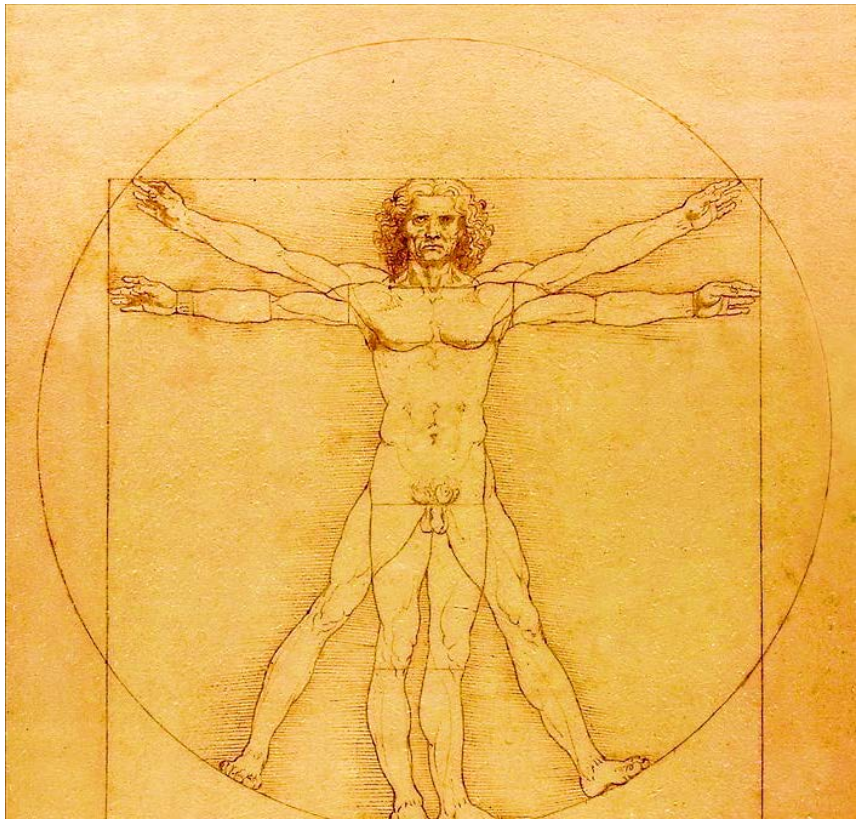
Transgenerational Effects

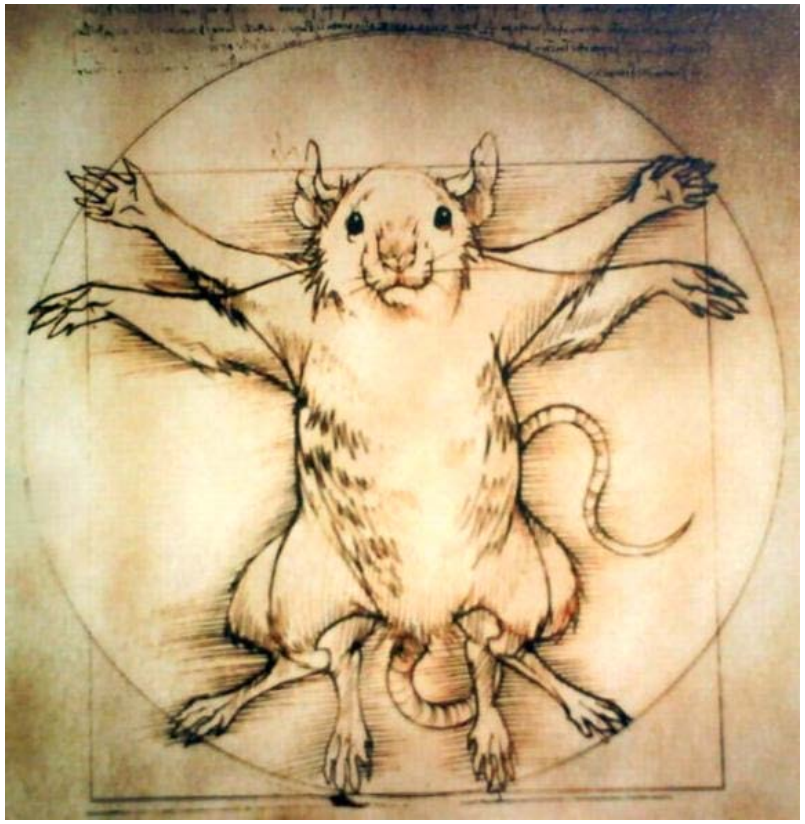


The effects of a single environmental exposure can be transmitted transgenerationally. An adverse maternal environment (F_0) effects not only the development of the fetus (F_1) but can also affect the germ cells which form the F_2 generation.

Vickers MH, Ann. Nutr. Metab. (2014)

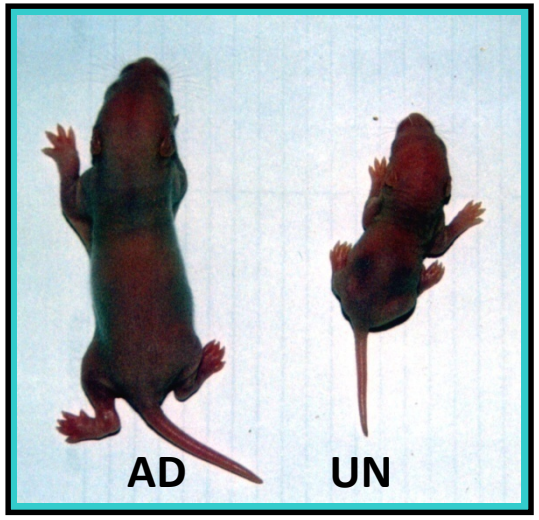
Animal Models

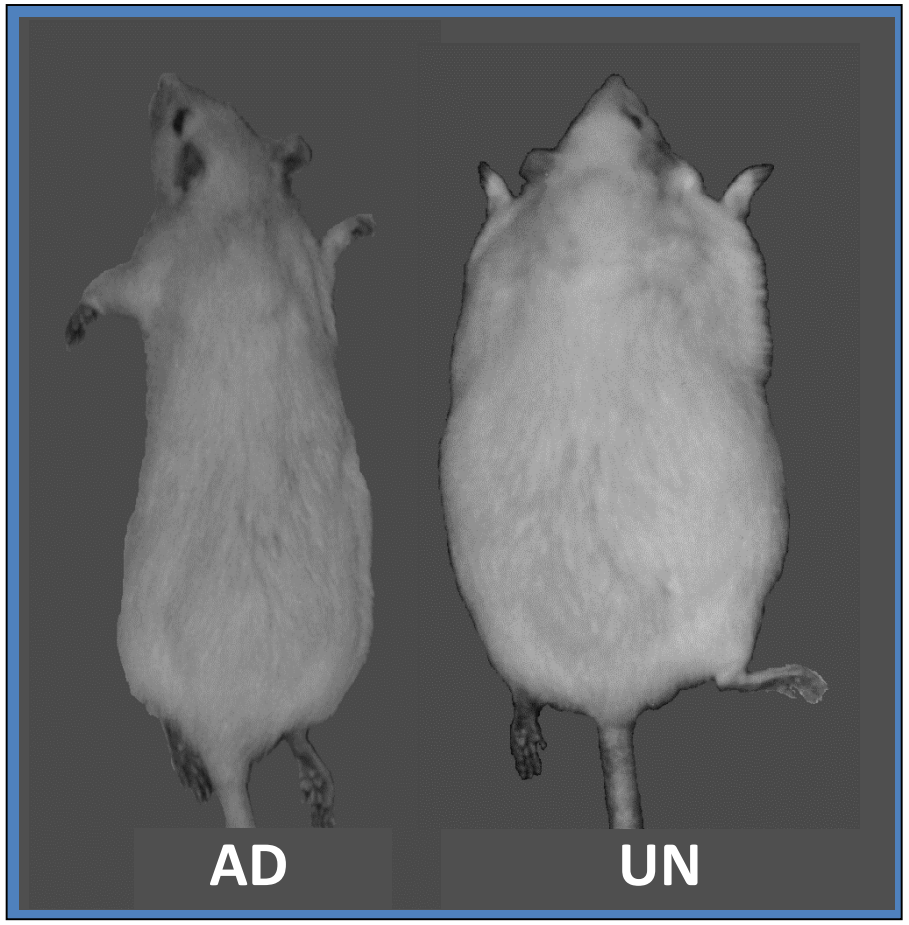




- use of pre-clinical models is essential to understand **mechanisms**, avenues for **intervention** strategies and **transgenerational** effects

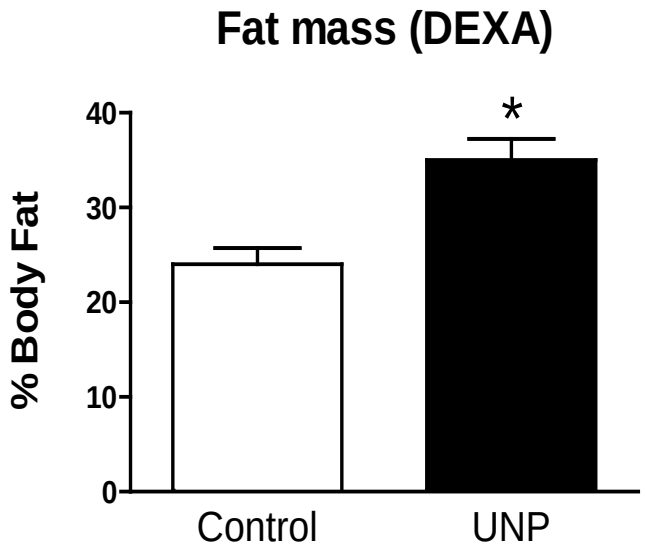
Maternal Undernutrition

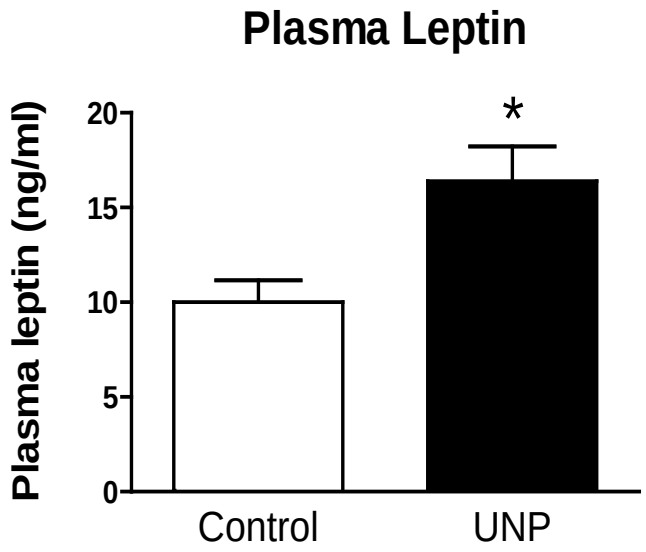


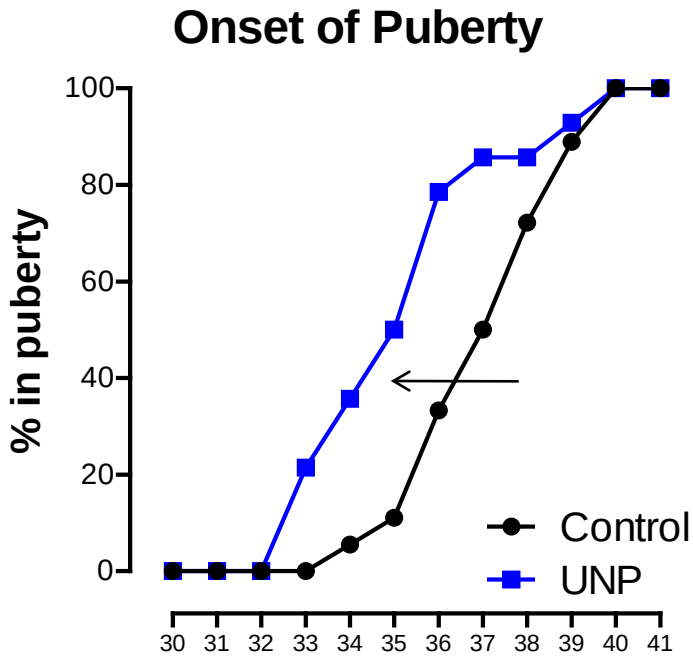


Moderate maternal undernutrition

- 50% of ad-libitum throughout pregnancy



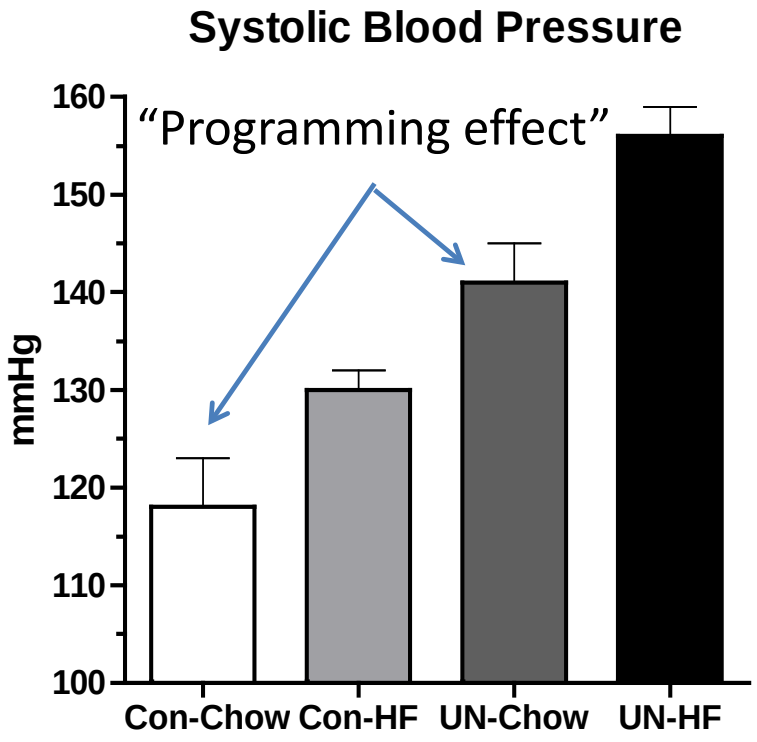


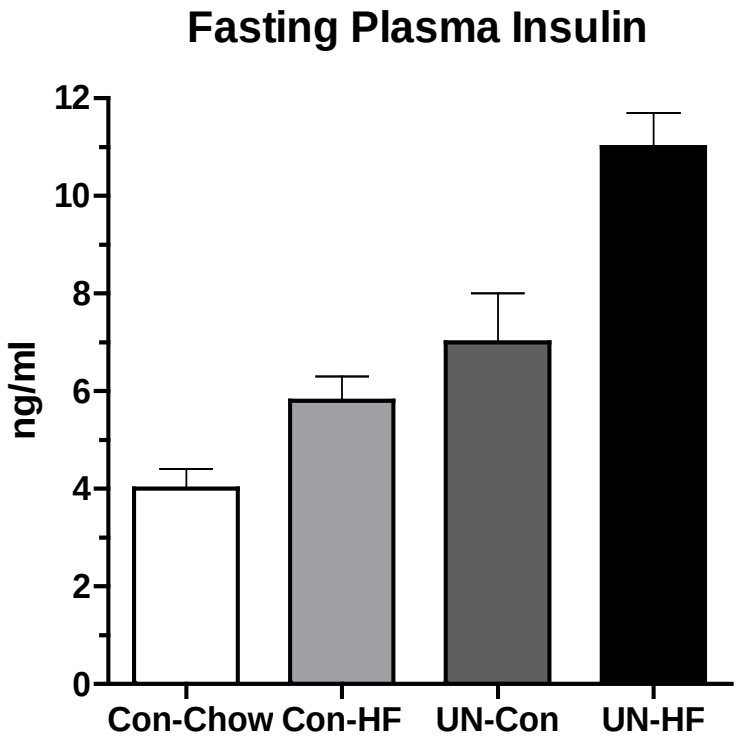


- Even moderate undernutrition in the rat induces significant obesity, hyperleptinemia and early onset puberty in offspring *independent* of postnatal diet

Howie & Vickers, Br. J. Nutrition, (2012)

Insulin resistance and hypertension in adult offspring



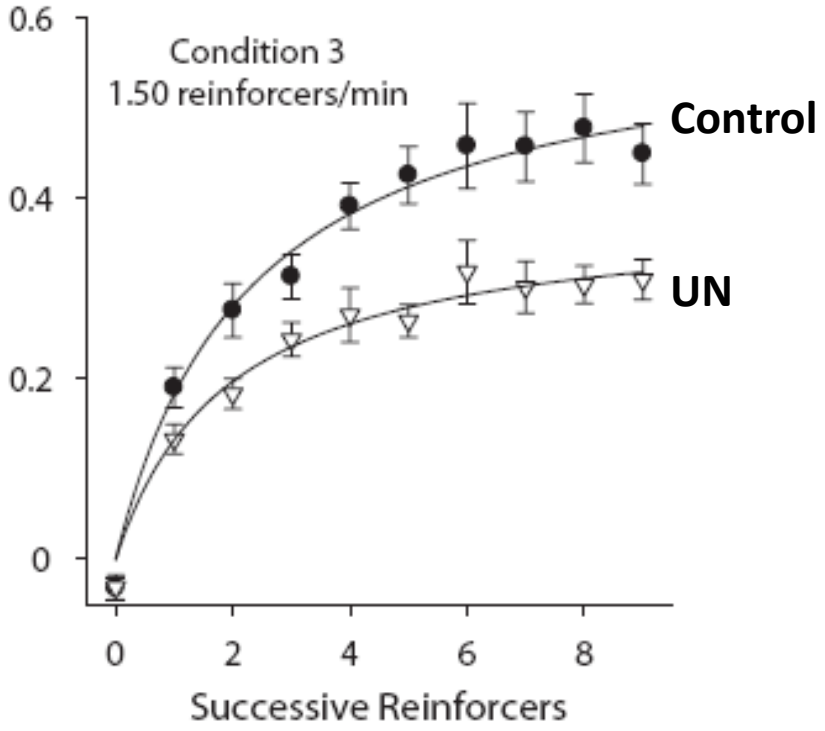


p<0.05 for effect of maternal diet and postnatal high fat diet

Vickers *et al*., Am. J Physiol. (2001)

Maternal Nutrition and Learning

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

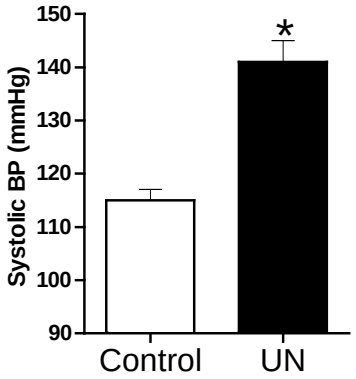


- this has been replicated in both animal and clinical cohorts

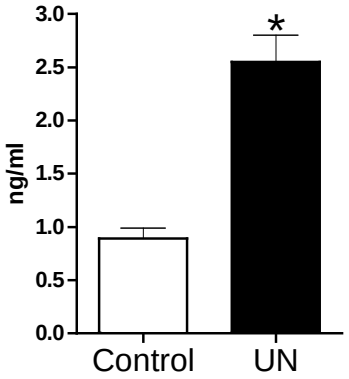
Landon J *et al*., Learn. Behav. 2007; 3592:79-86

Programming in offspring following Maternal Undernutrition

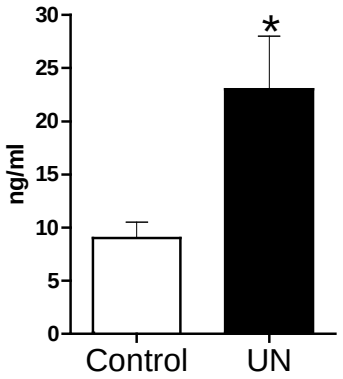
Blood pressure



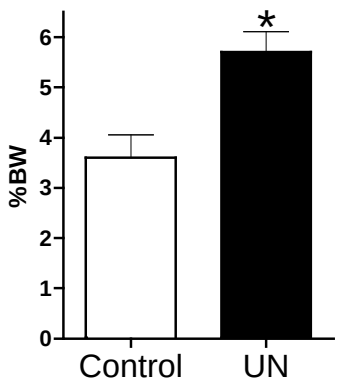
Insulin



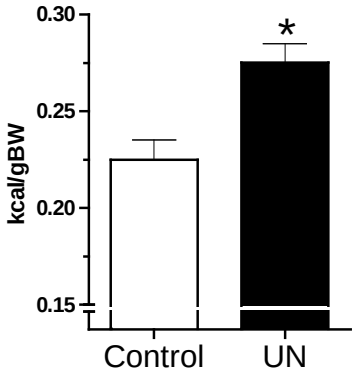
Leptin



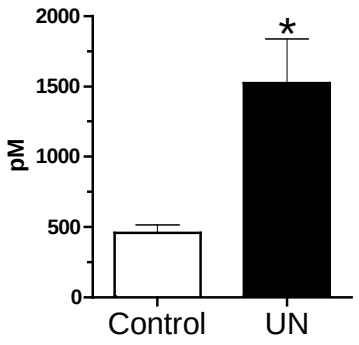
Fat Pad (%)



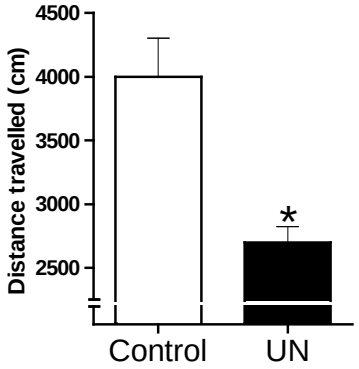
Intake



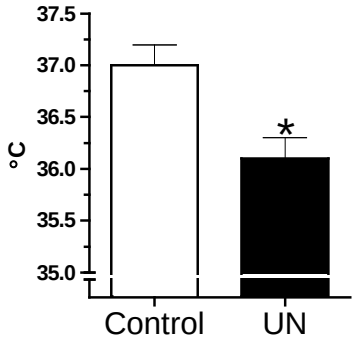
C-Peptide



Activity



R. Temp



Reduced lifespan

* p< 0.05 for maternal diet effect

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Maternal Obesity

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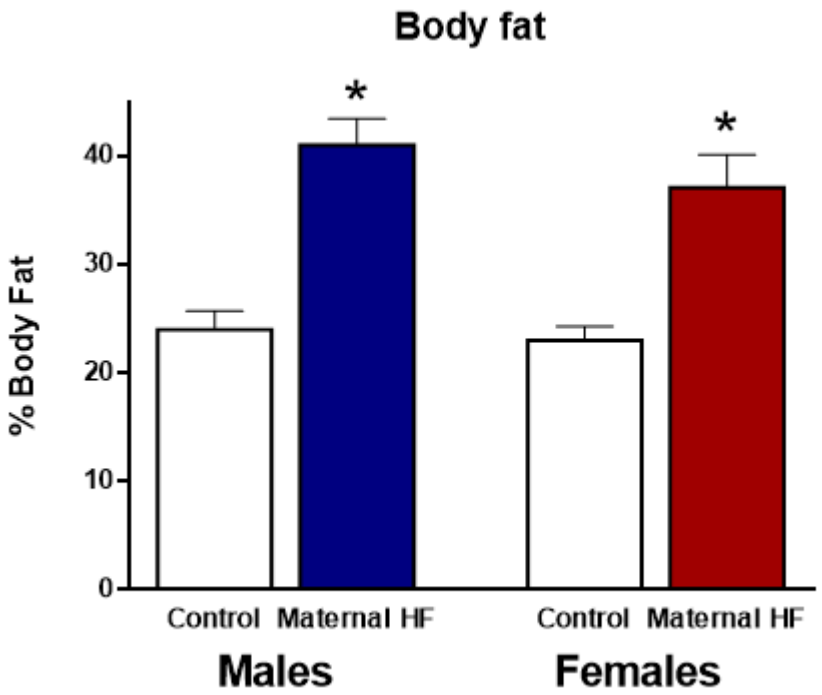
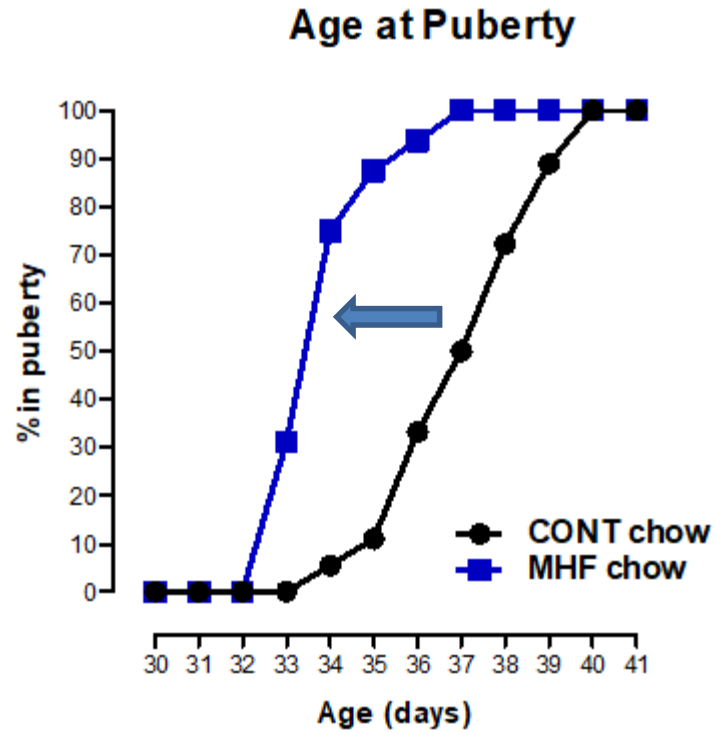
Maternal Obesity = Offspring Obesity



Offspring

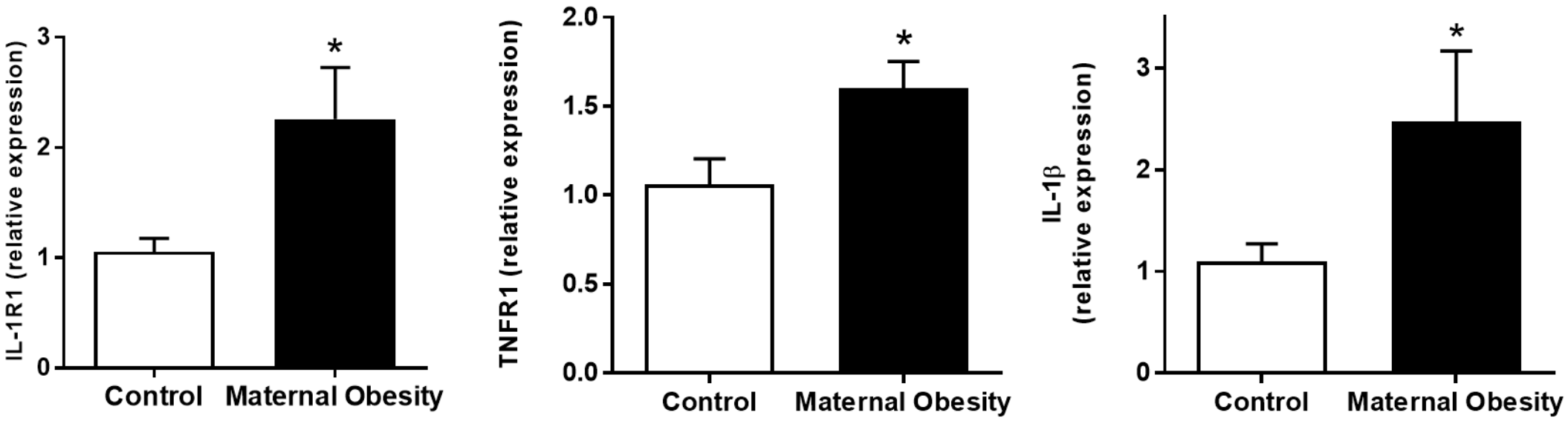
Control Maternal HF



- 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

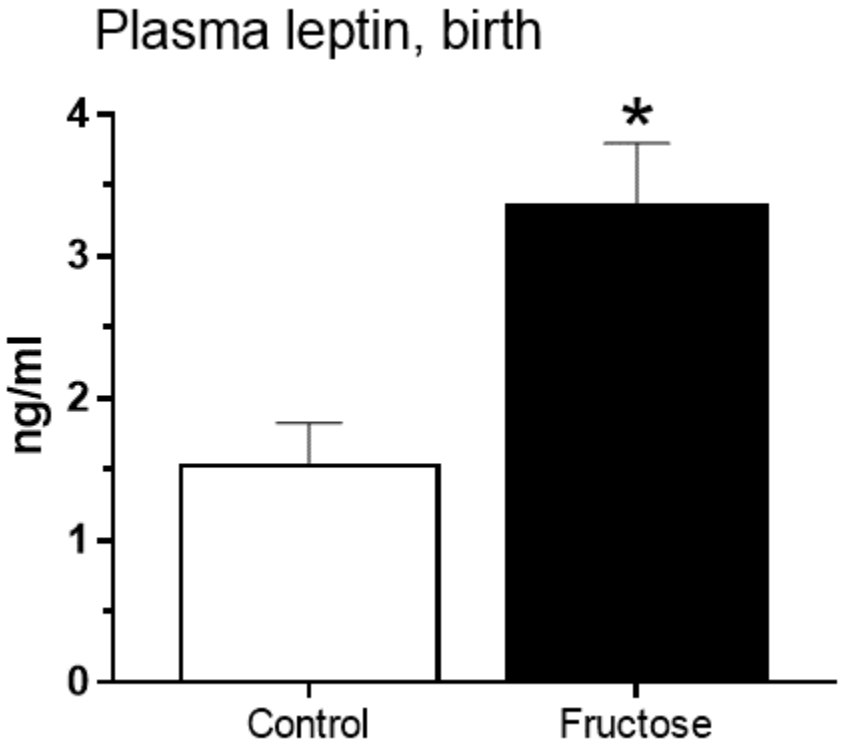
Maternal obesity and inflammation in offspring at birth



- Maternal obesity leads to increased inflammation in livers of offspring **<u>at birth</u>**

Li, Vickers, Reynolds *et al.*

Maternal Sugar Intake



Increased maternal sugar intake results in hyperleptinemia in offspring *at birth*

Vickers et al., Endocrinology 2011, Vickers et al. PLoS One 2015

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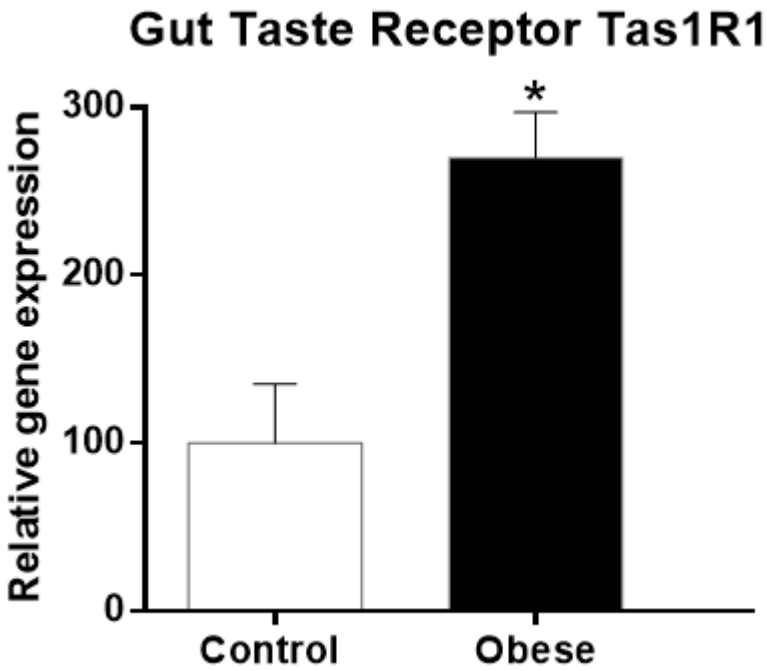
What determines our health potential?

Can be “programmed” in the first 1000 days

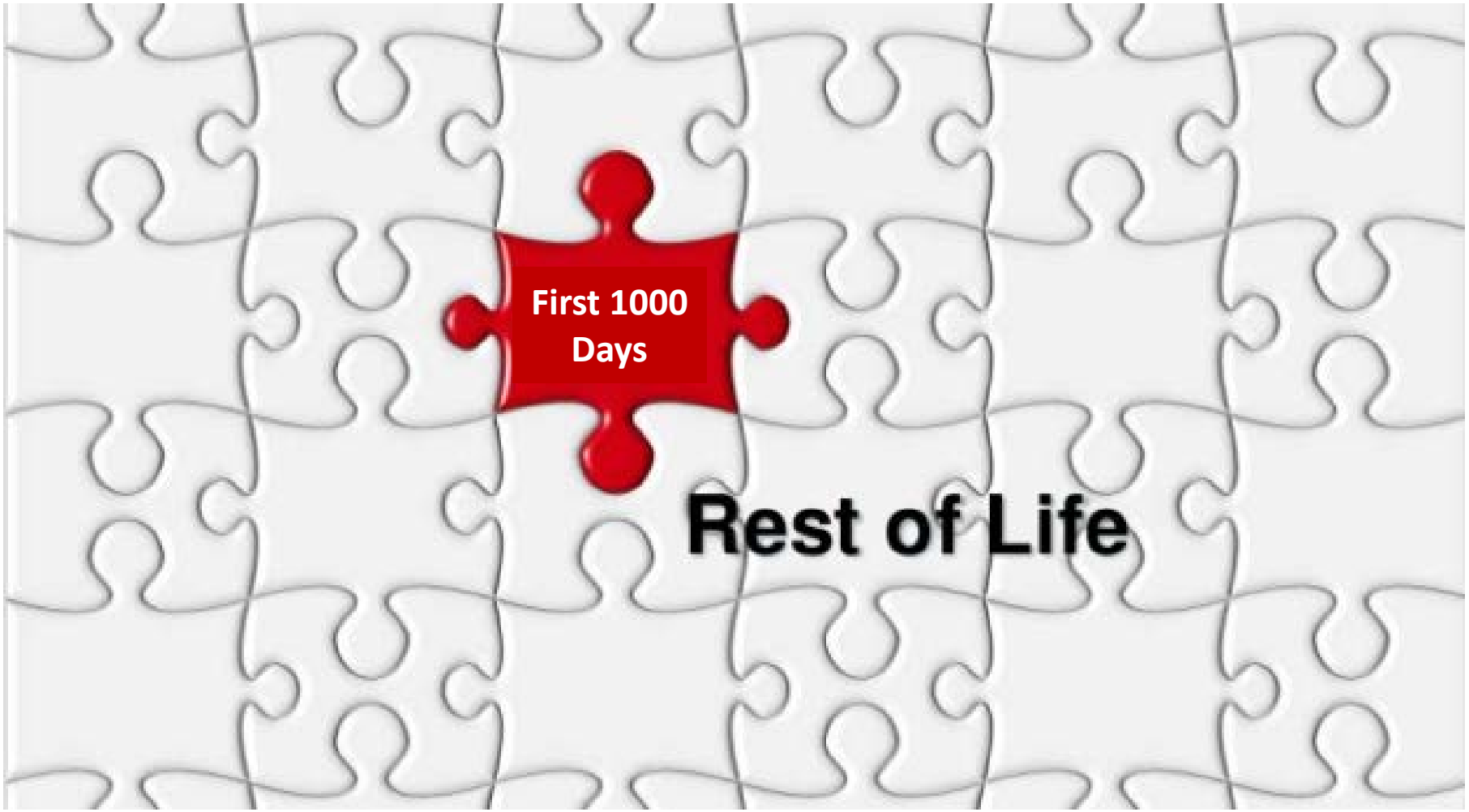
Programming of taste receptors and appetite



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

Reynolds and Vickers *et al. Physiol Rep. 2015;3(10). pii: e12588*

Can programming be prevented via early life nutritional modifications ?



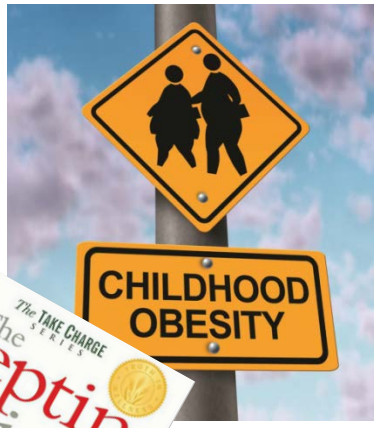
Modified from Stefan Johansson, Karolinska Institute Sweden

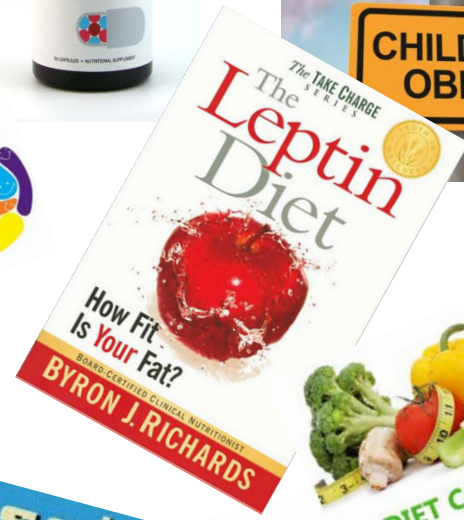
What interventions ?

- 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





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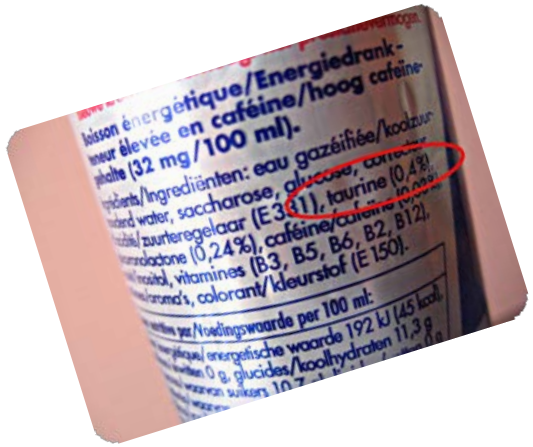
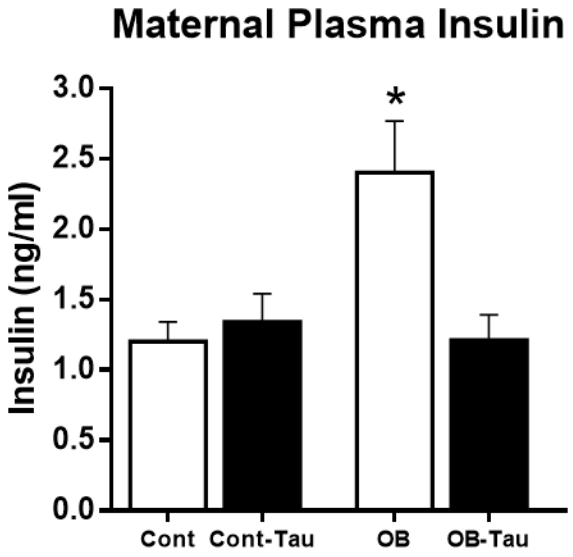
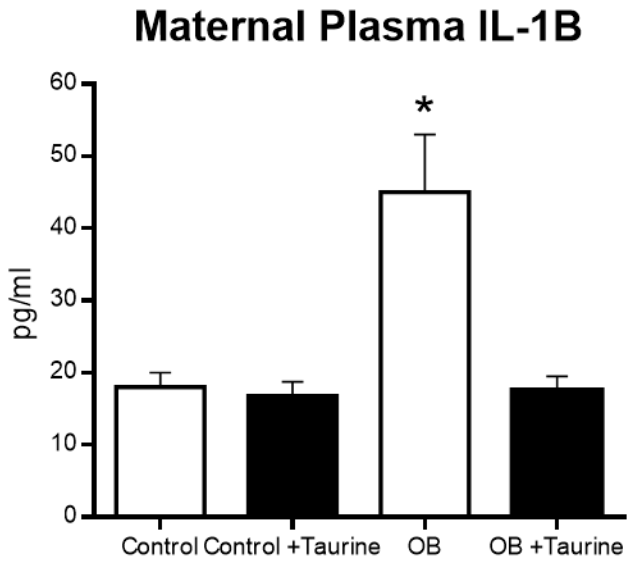
Maternal Taurine Supplementation

Obese mothers







- obese mothers are hyperinsulinemic compared to lean control mothers with increases in inflammatory markers

- these effects are normalised with maternal taurine supplementation

Vickers, Li et al (J. Nutr. Biochem, 2015)

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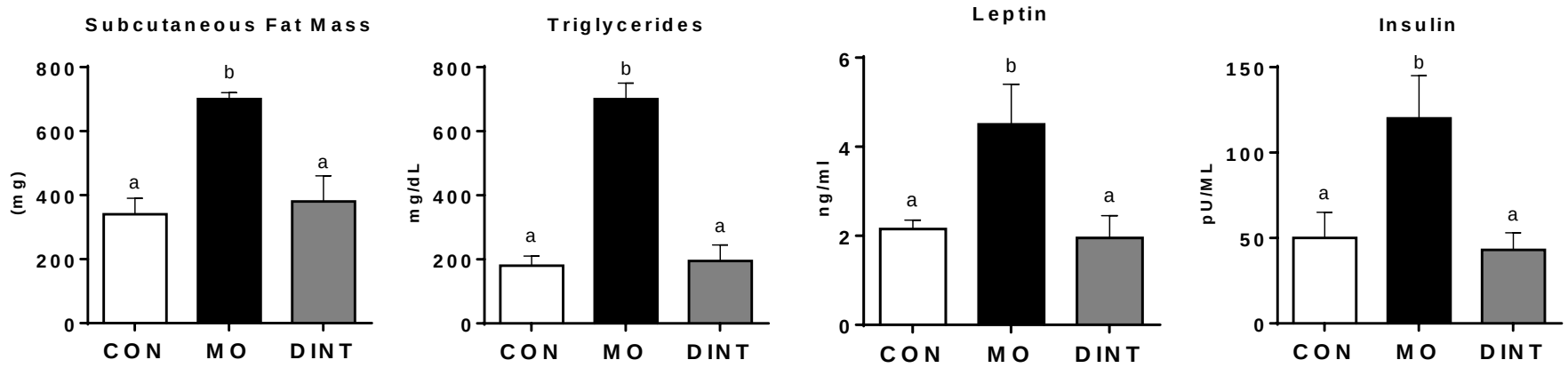
Dietary intervention in obese mothers *prior* to pregnancy

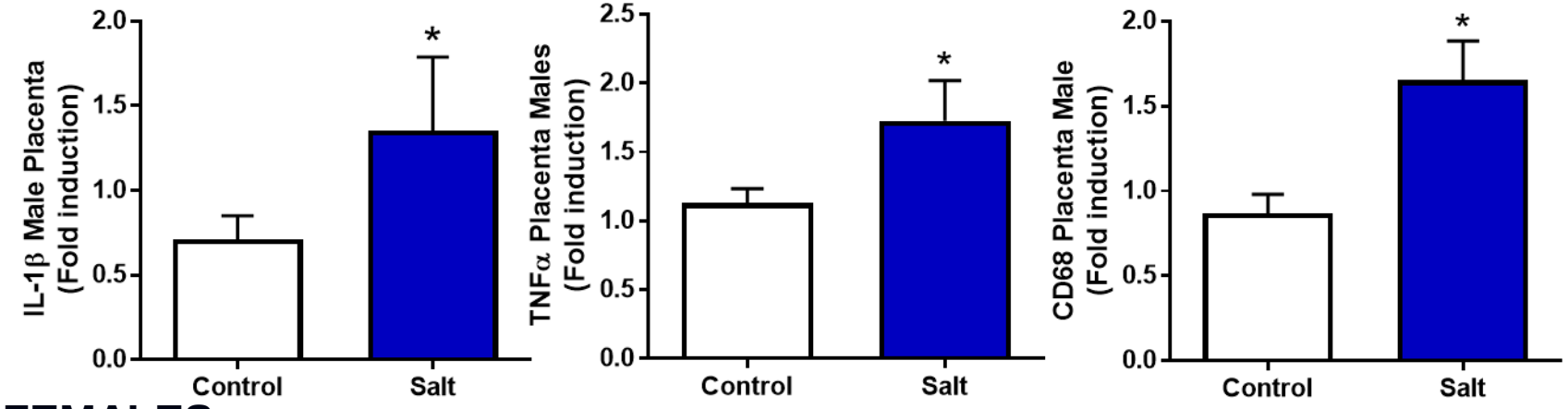


- dietary intervention in obese mothers 4 weeks prior to conception
- reversed metabolic programming in offspring of obese mothers
- effects persisted into adult life

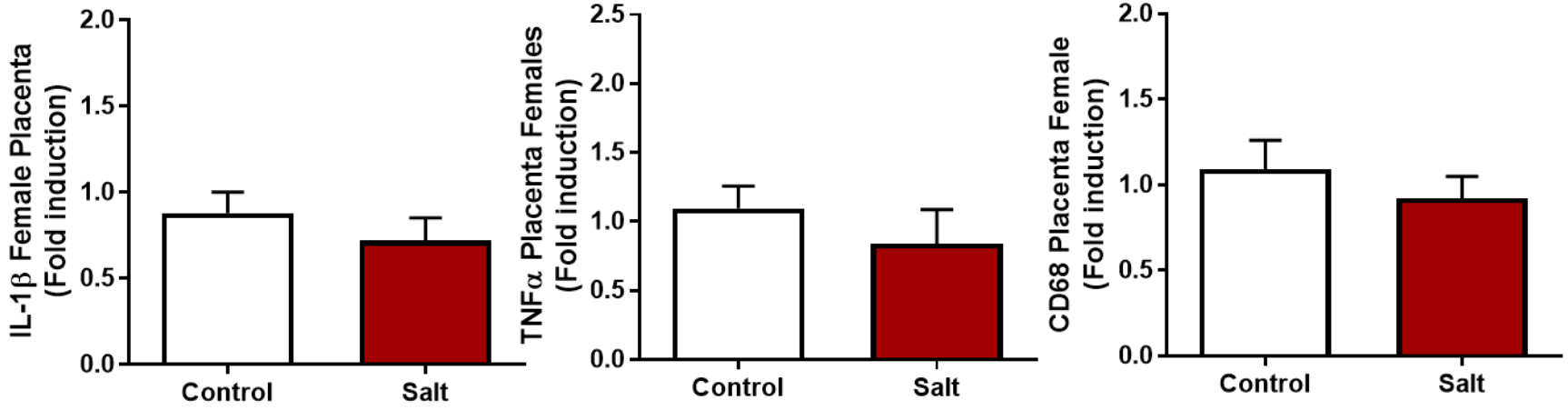
Zambrano *et al.*, J Physiol, 2010

Sex-specific Effects

MALES



FEMALES



Reynolds, Vickers *et al*., Physiol. Reports, 2015.

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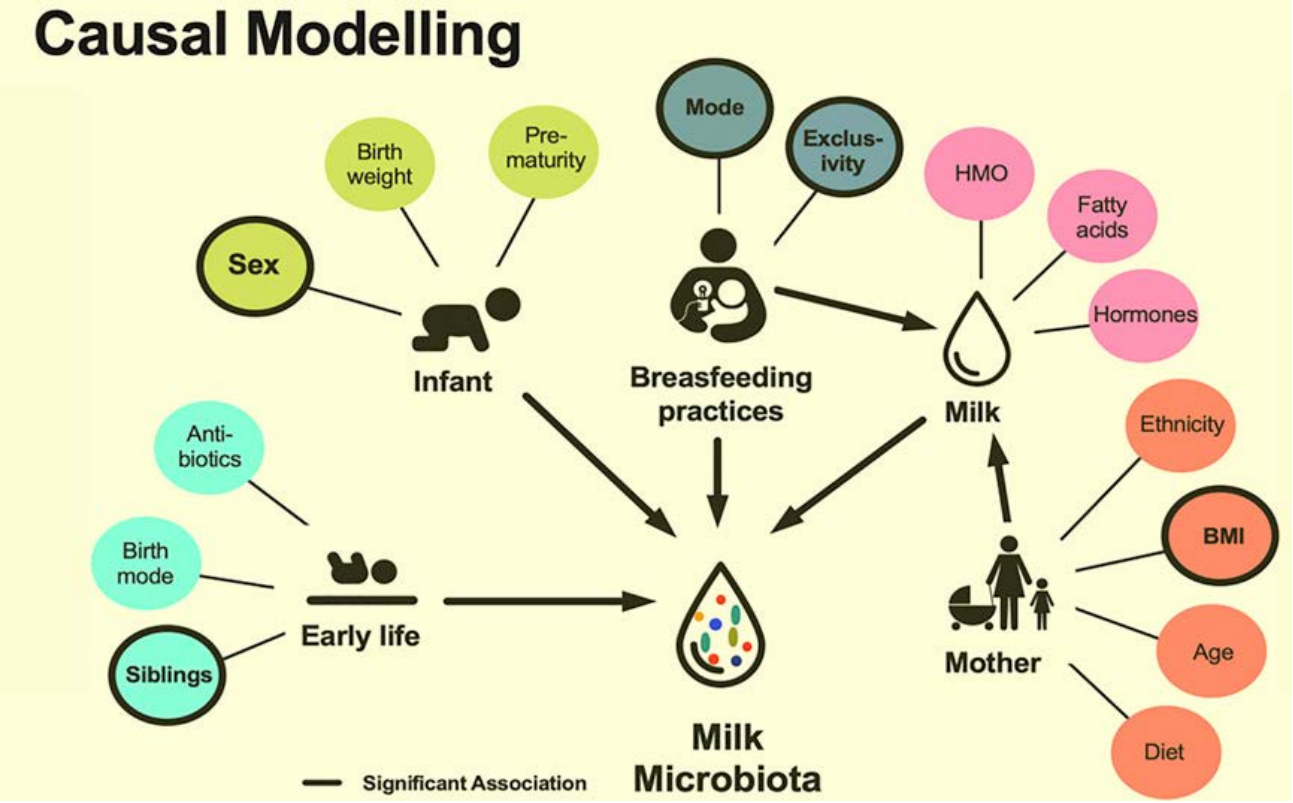
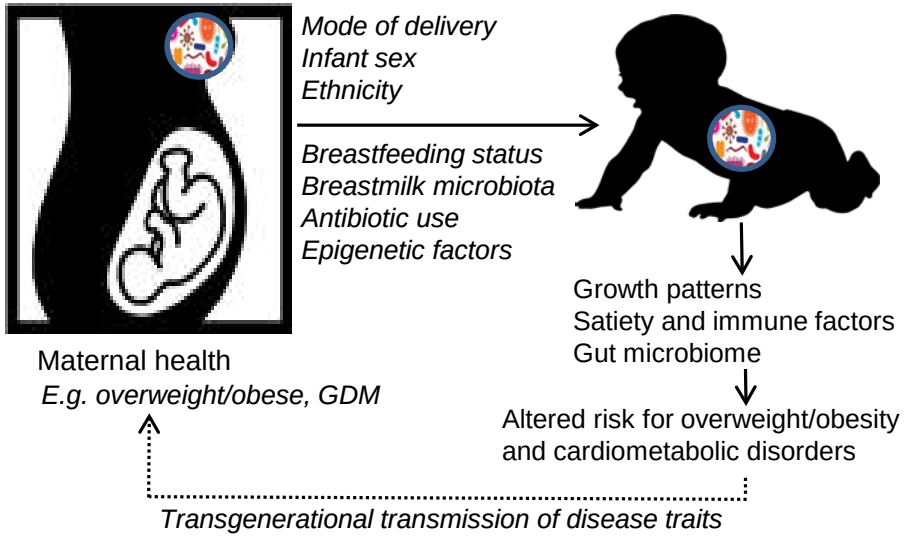
Maternal nutrition and the breast milk and infant microbiome





Cell Host & Microbe
Volume 25, Issue 2, 13 February 2019, Pages 324-335.e4

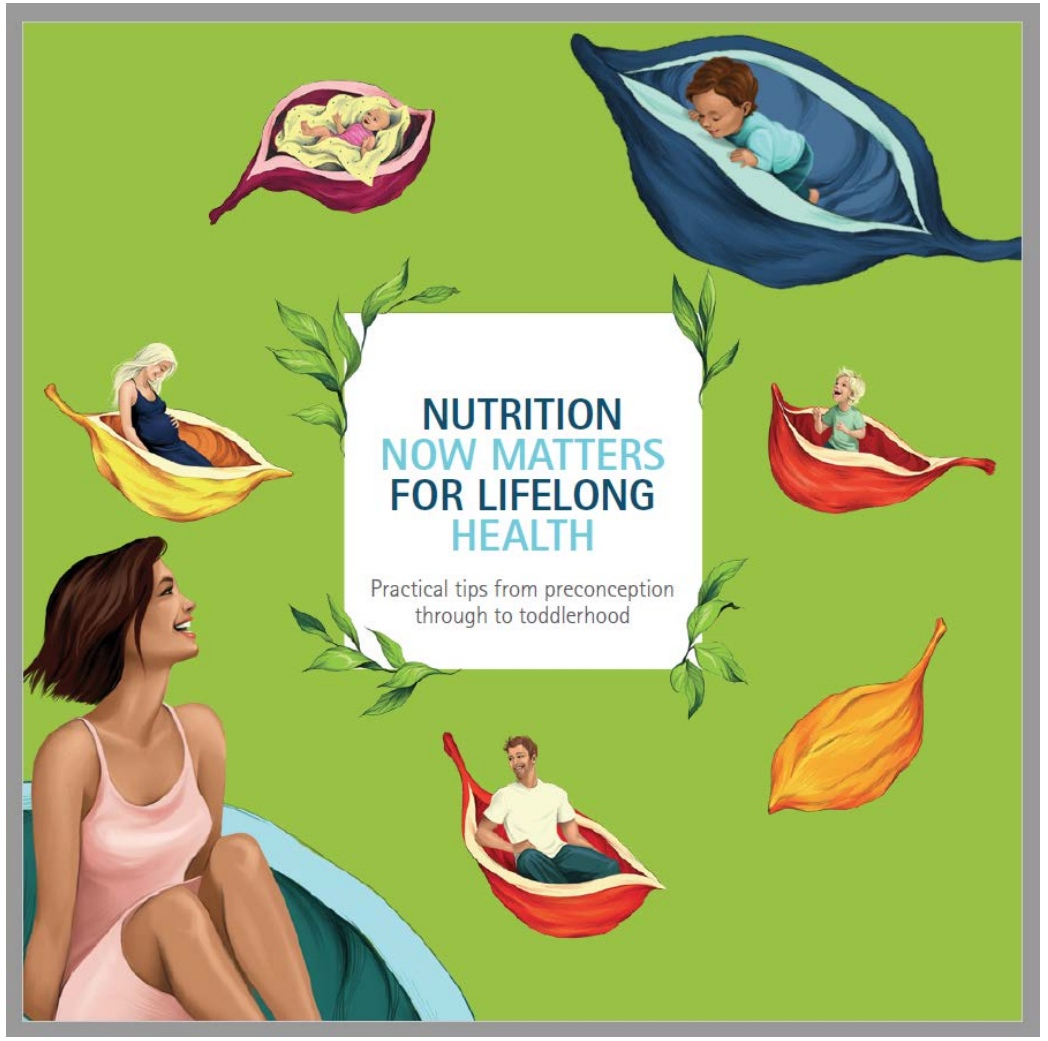
Article

Composition and Variation of the Human Milk Microbiota Are Influenced by Maternal and Early-Life Factors

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
A CRITICAL WINDOW OF OPPORTUNITY

J Dev Orig Health Dis. 2016 Oct;7(5):440-448. Epub 2016 Jan 26.

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

Davies PS[1], Funder J[2], Palmer DJ[3], Sinn J[4], Vickers MH[5], Wall CR[6]; as the Australia and New Zealand Early Life Nutrition Working Party.

https://elnc.psanz.com.au/

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Discussion

Pre-conception +

- 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