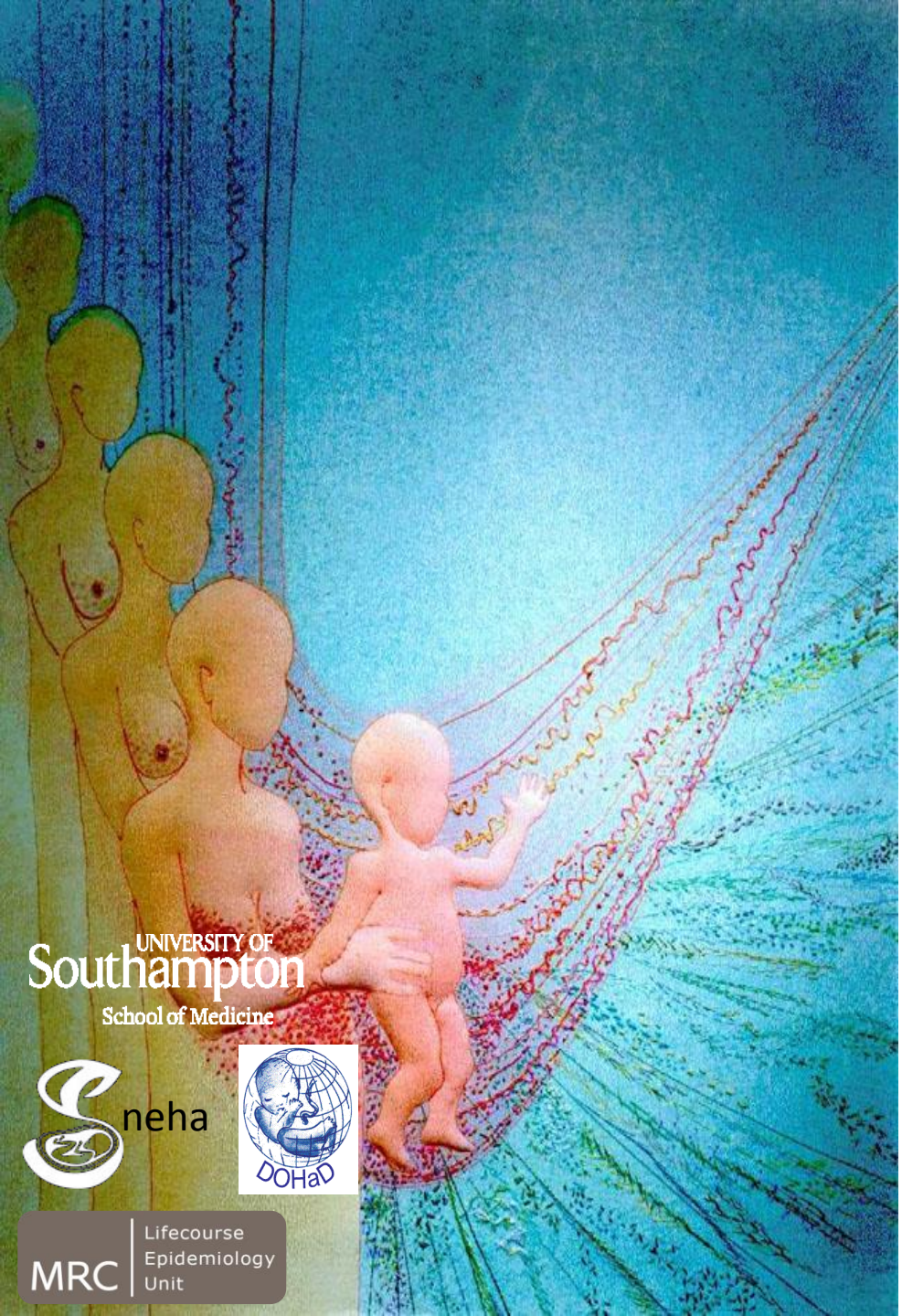


Caroline HD Fall

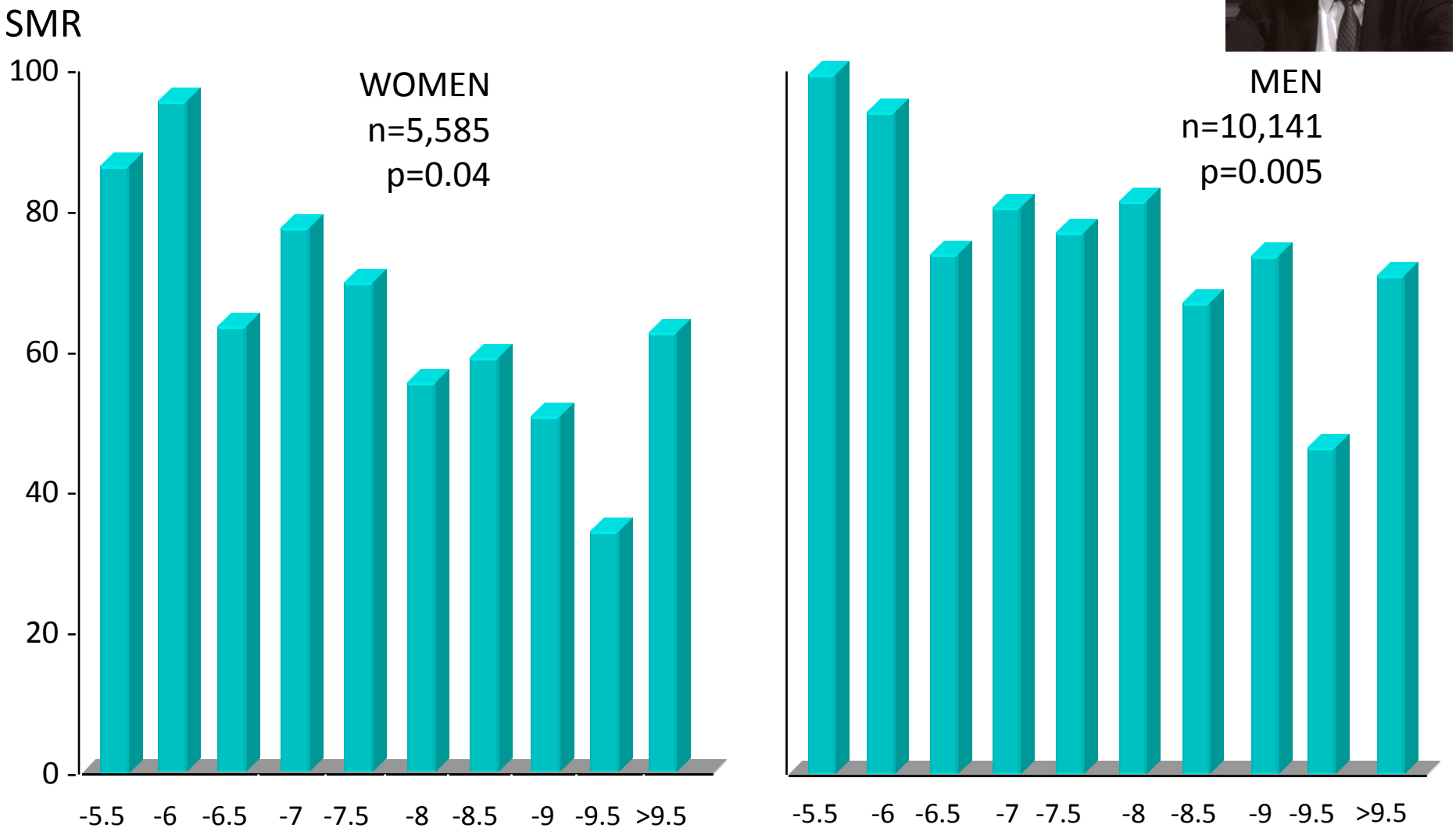
MRC Lifecourse Epidemiology Unit
University of Southampton
chdf@mrc.soton.ac.uk

Early life nutrition: the origins of cardiovascular disease?

British Nutrition Foundation
27th February 2019

Cardiovascular Disease Mortality

Men and women born in Hertfordshire 1911-1930



BMJ 1993; 307:1519

The ‘Barker Hypothesis’

Fetal and early post-natal development is an orchestrated process - everything must happen in sequence and at the right time (‘critical periods’).

It’s moulded by the maternal environment, including nutrition, hormones, toxins, stress.

Many ‘metabolic’ tissues are fixed by birth and deficits can be permanent, and cause disease.

Undernourished mother

Mother can't mobilise and transport nutrients

Impaired 'supply line' womb, placenta, blood flow

FETAL AND INFANT UNDERNUTRITION

Inadequate 'building blocks'

Adaptation to reduce demand

Liver

↓ Insulin sensitivity

Pancreas

↓ Insulin secretion

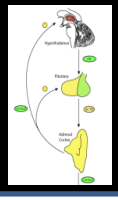
Muscle, Fat, Bone

↓ Muscle
↑ Fat
Insulin resistance

Brain

Altered appetite centres

Hormones



↑ Cortisol

Kidney

↓ Nephrons

Blood vessels

↓ Elasticity

Heart

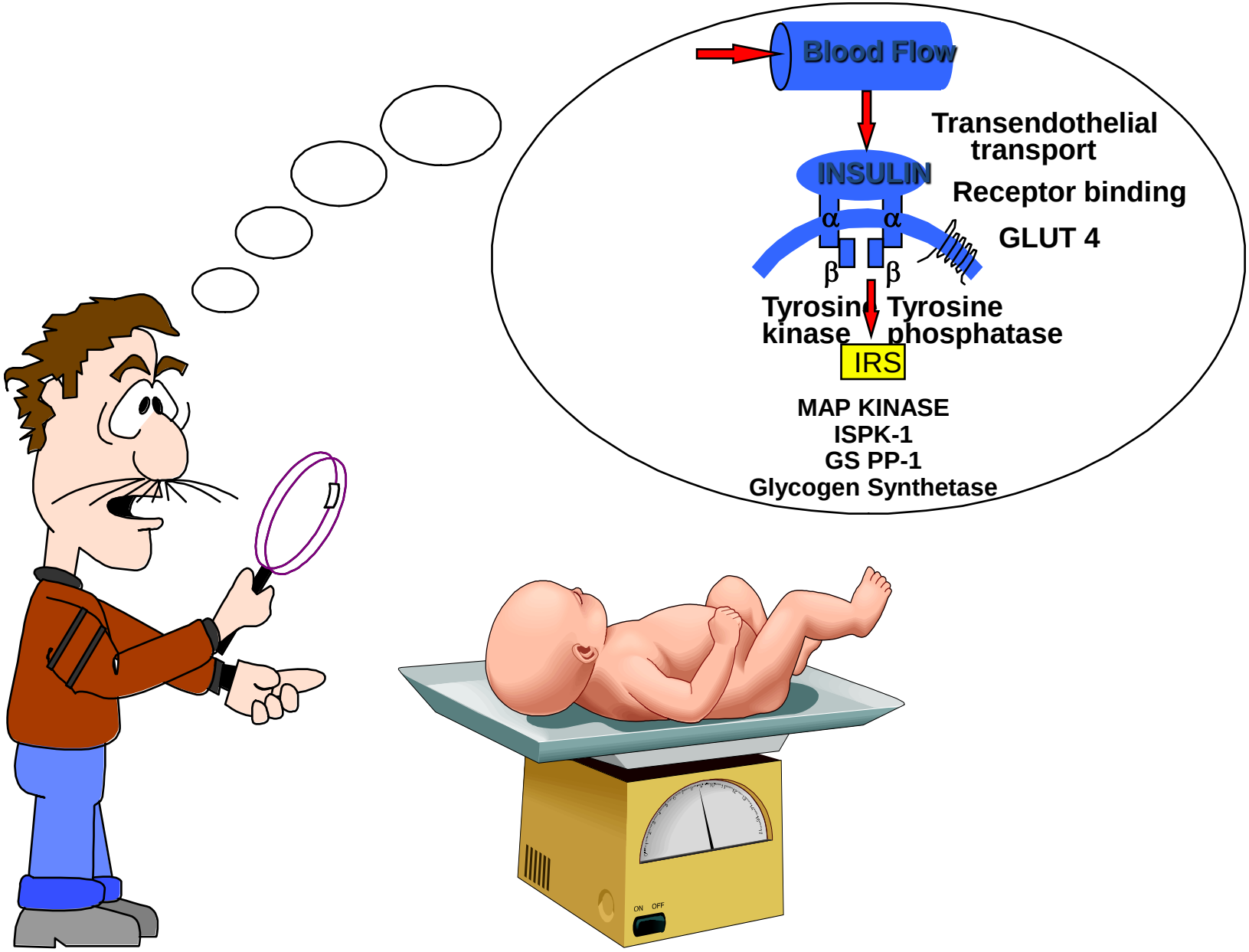
↓ Muscle

High cholesterol

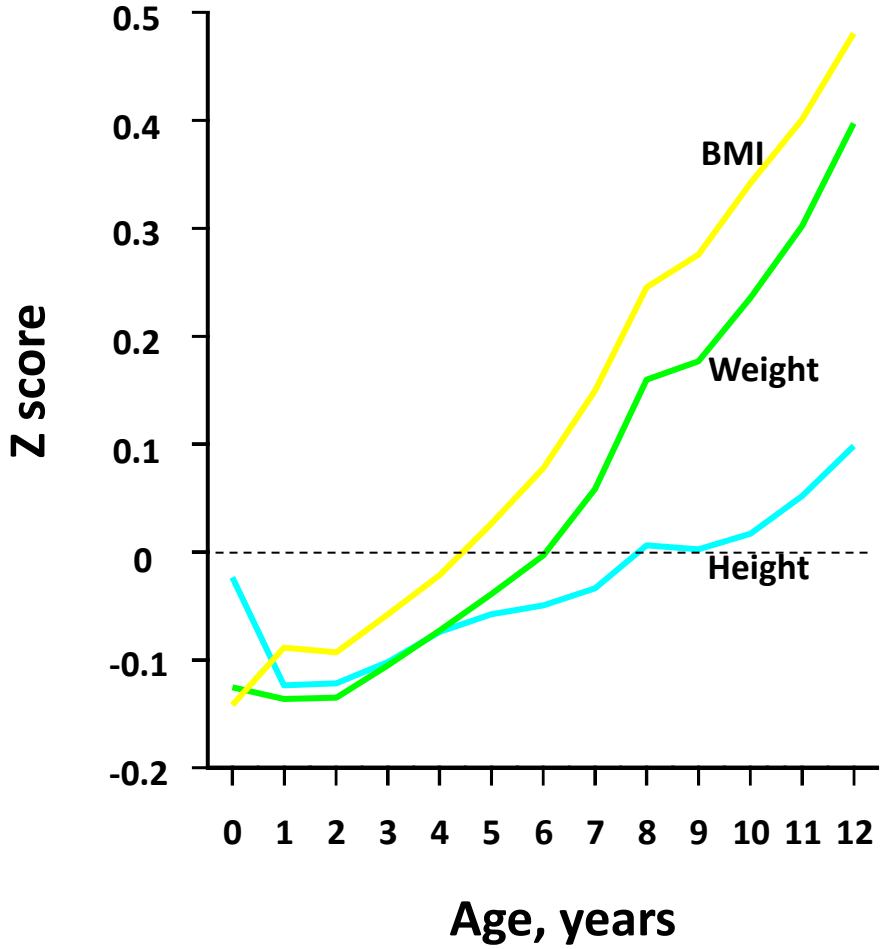
Diabetes

Hypertension

Coronary heart disease

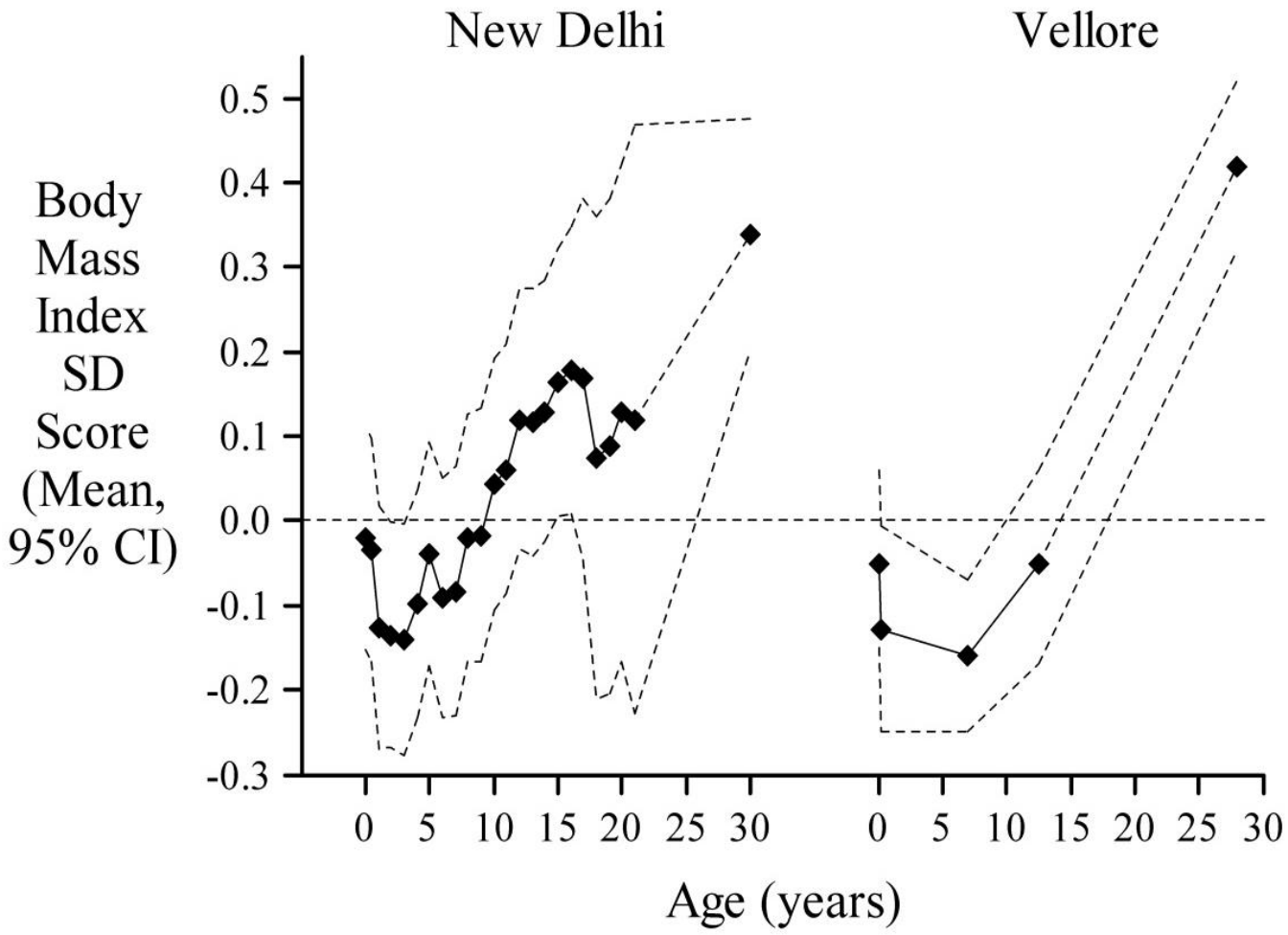

Blood Flow
Transendothelial transport
INSULIN
Receptor binding
α
α
GLUT 4
β
β
Tyrosine kinase
Tyrosine phosphatase
IRS
MAP KINASE
ISPK-1
GS PP-1
Glycogen Synthetase
ON
OFF

Childhood growth of 290 men and women with Type 2 diabetes from a cohort of 8760, Finland



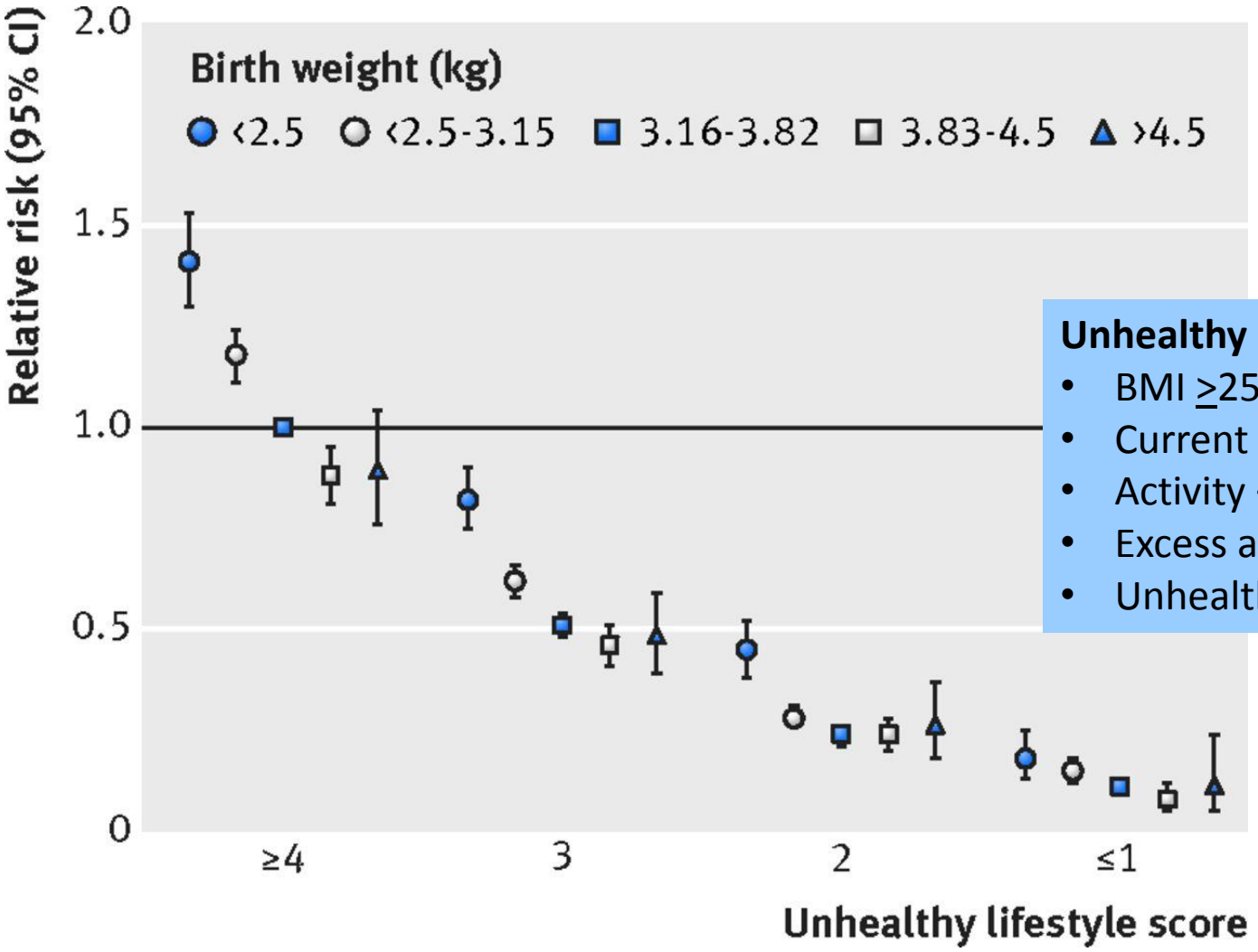
Eriksson JG et al Diabetologia 2003;46:190-194

BMI from birth to adulthood for men and women who developed adult pre-diabetes or diabetes



Type 2 diabetes risk according to birth weight and unhealthy adult lifestyle score

Health Professionals Follow-up Study and Nurses' Health Study (3 million person years)

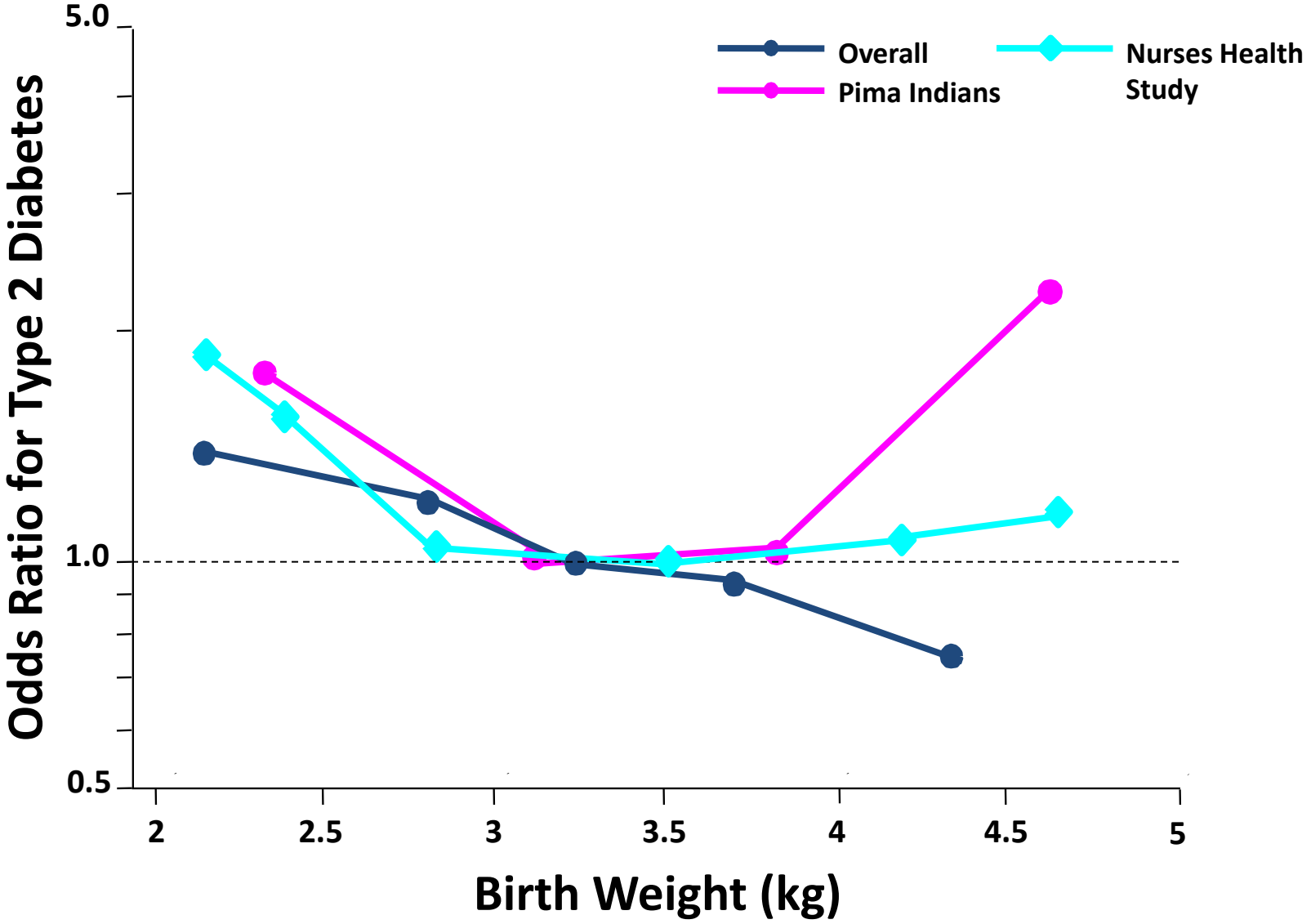


Unhealthy lifestyle score

- BMI ≥25
- Current smoker
- Activity <30 min/day
- Excess alcohol
- Unhealthy diet

Yanping Li et al. BMJ 2015;351:bmj.h3672

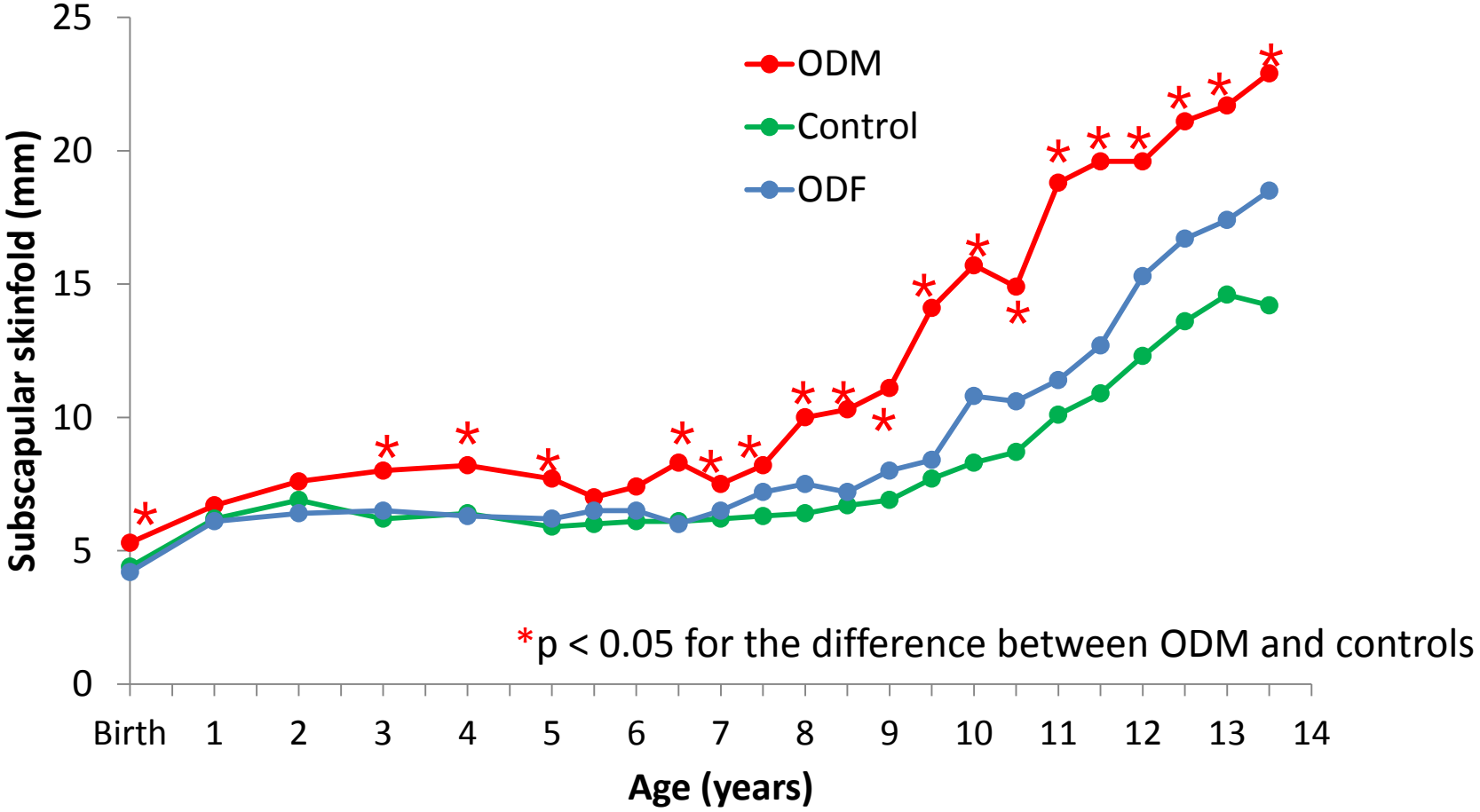
Birthweight and type 2 diabetes



Whincup P et al. Earlyread collaboration JAMA 2008; 300: 2886-97

Mysore Parthenon Study

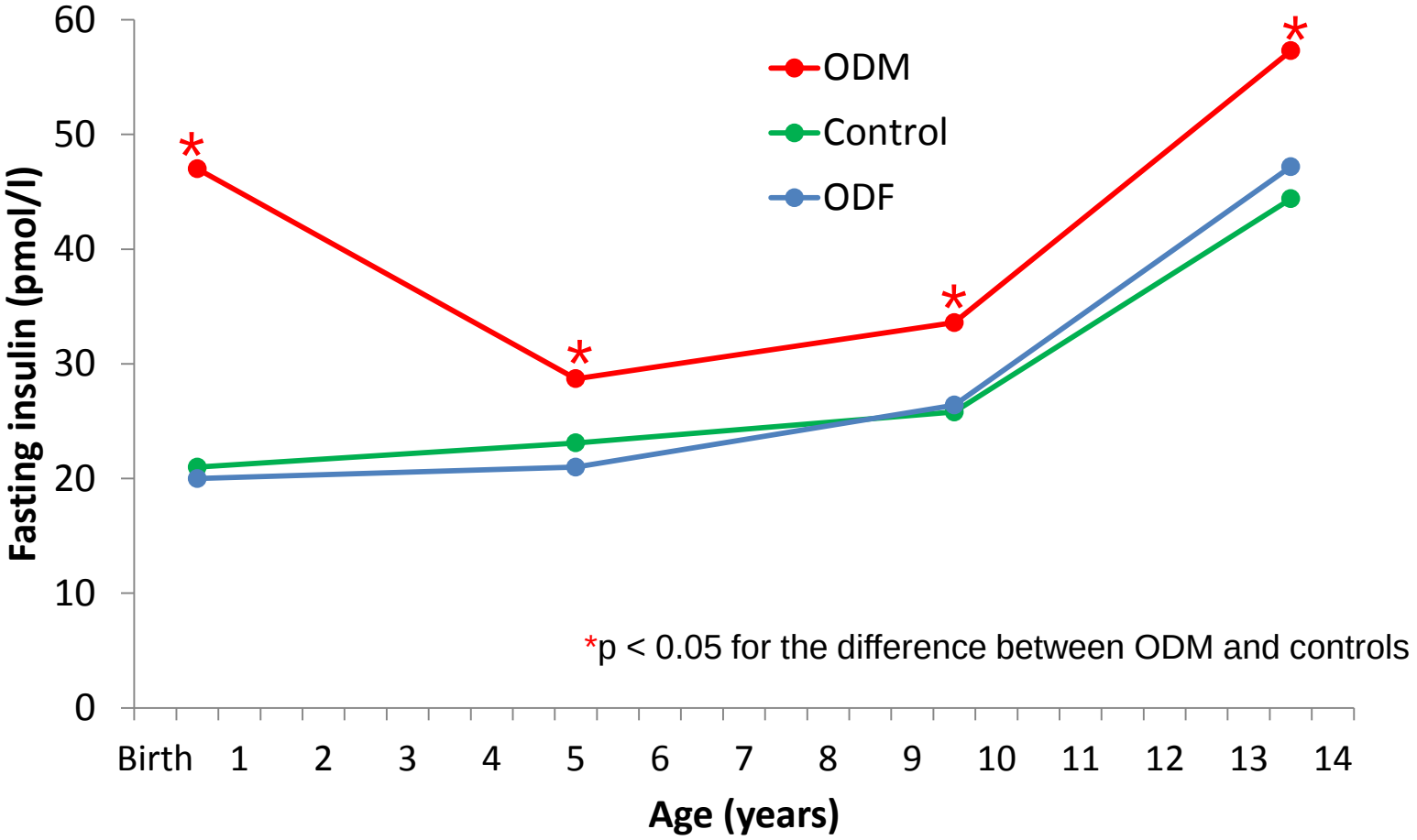
Adiposity (girls)



Krishnaveni GV Diabetes Care 2005; 28: 2919-25 and *Diabetes Care* 2010; 33: 402-4

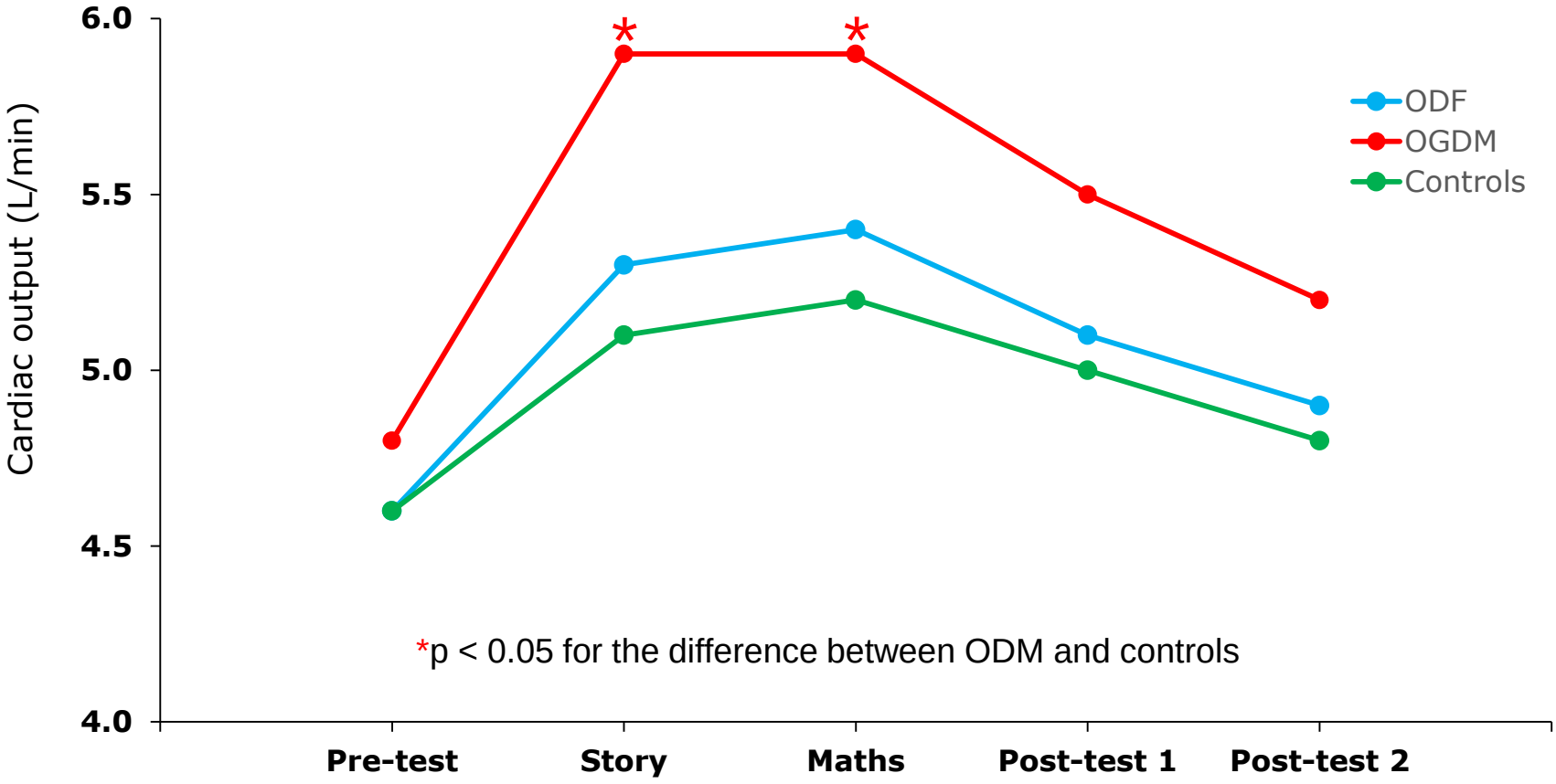
Mysore Parthenon Study

Fasting insulin (girls)



Krishnaveni GV Diabetes Care 2005; 28: 2919-25 and *Diabetes Care* 2010; 33: 402-4

Mysore Parthenon Study
Cardiac output during stress test



Krishnaveni GV J Clin Endocrinol Metab 2015; 100:986-93

Other early life exposure associated with later cardio-metabolic outcomes

Maternal exposures

- Pre-eclampsia (high blood pressure and lower cognitive function)
- Smoking (obesity)
- Corticosteroids (high blood pressure, plasma insulin, obesity)
- Stressful events (stress responses)
- Endocrine disrupting chemicals (obesity)

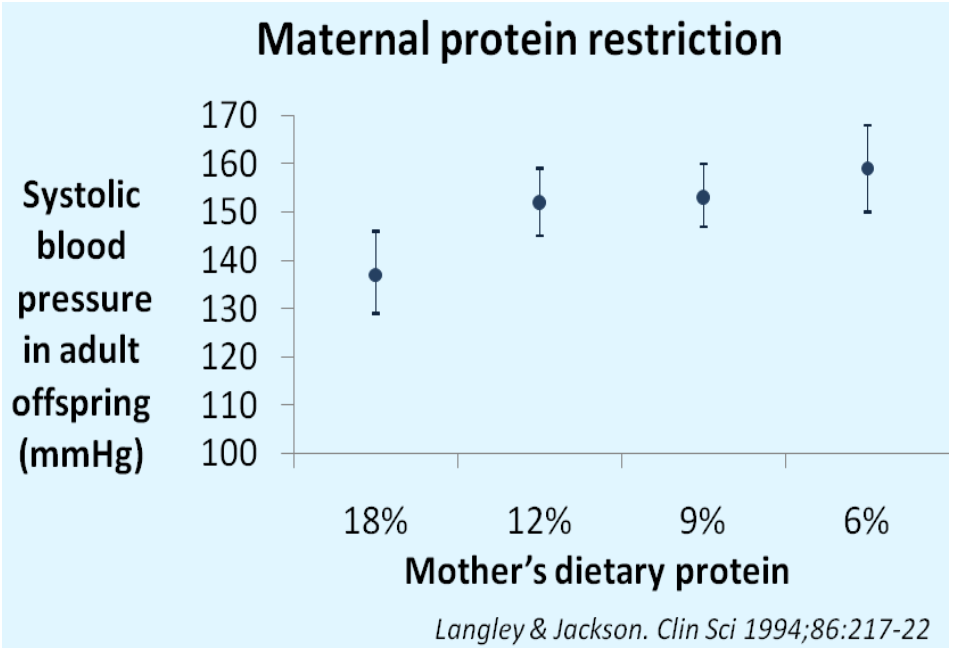
Infant exposures

- Formula v breastfeeding (obesity, diabetes, hypertension, raised cholesterol)
- Early weaning (obesity)
- Stressful events (high blood pressure, altered stress responses)

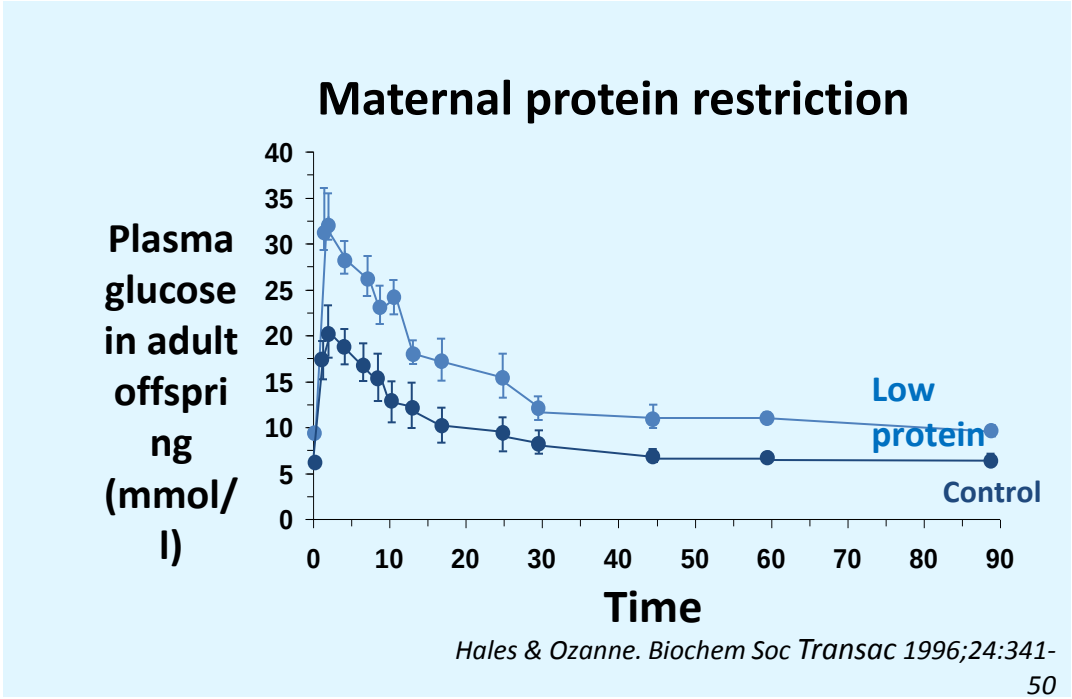
In rats, maternal protein restriction in pregnancy leads to:

- Raised blood pressure
- Increased adiposity
- Insulin resistance
- Glucose intolerance

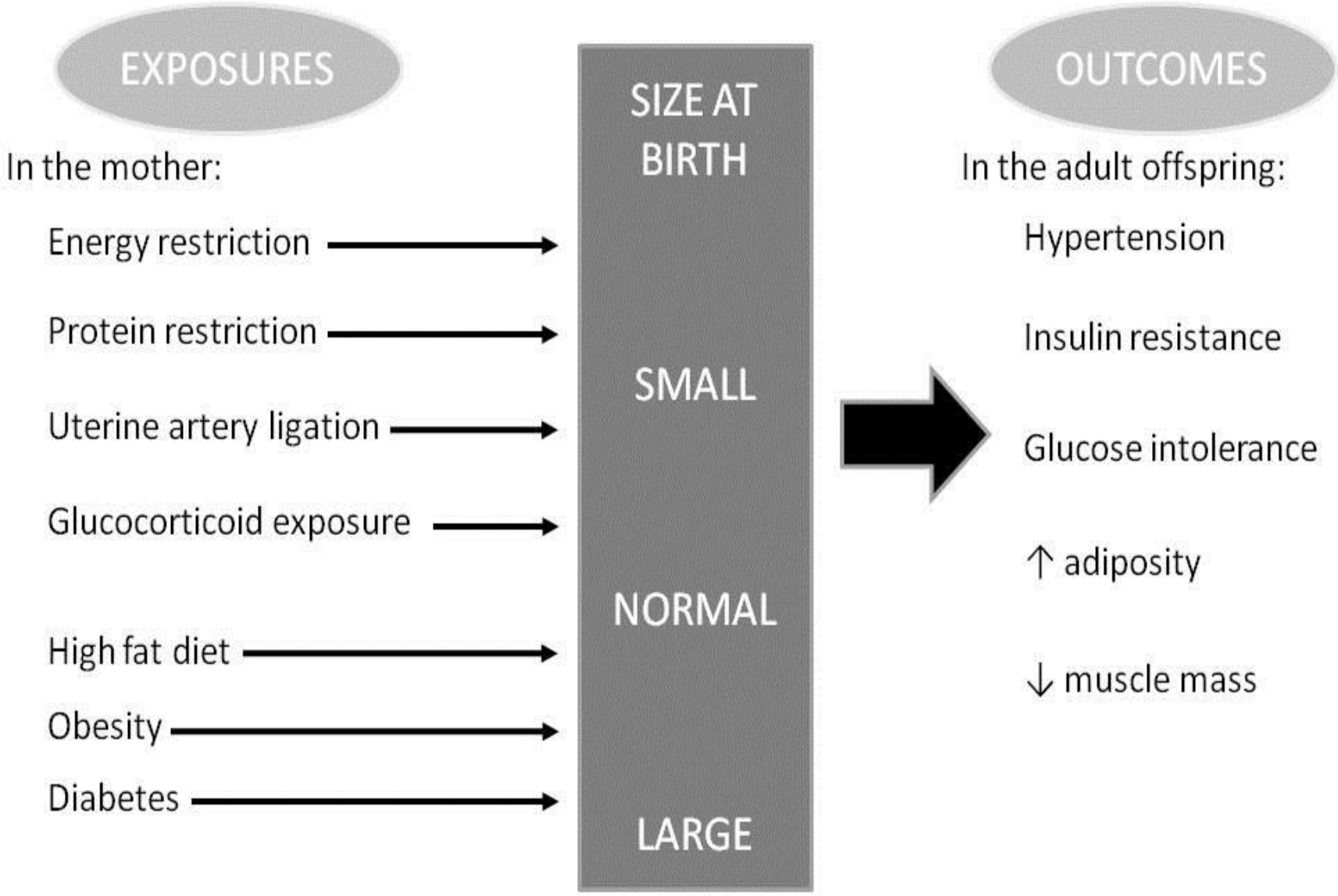
in the adult offspring



Langley & Jackson. Clin Sci 1994;86:217-22

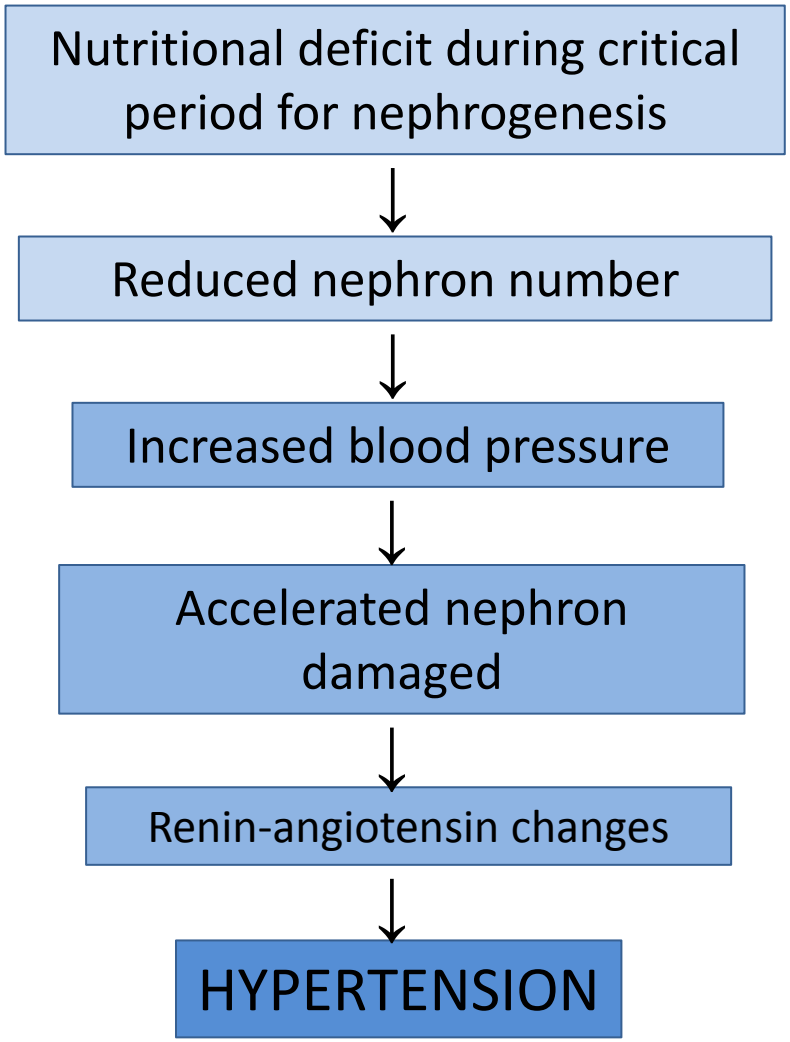


Hales & Ozanne. Biochem Soc Transac 1996;24:341-50

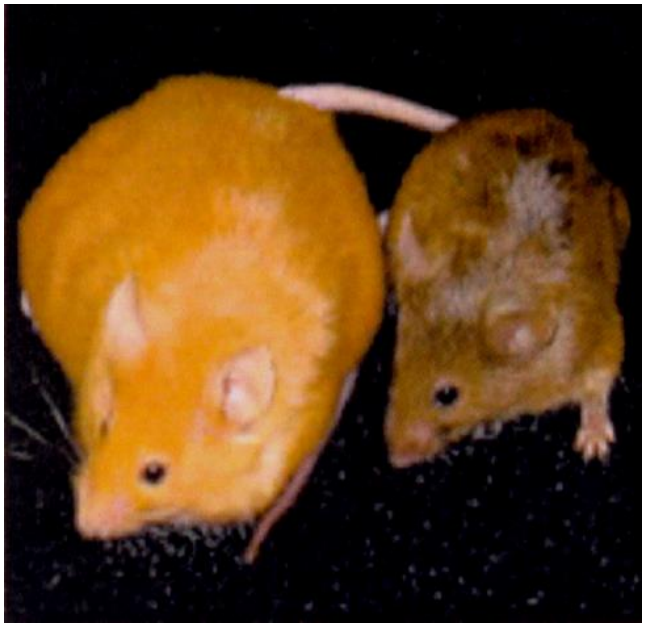

EXPOSURES
In the mother:
Energy restriction
Protein restriction
Uterine artery ligation
Glucocorticoid exposure
High fat diet
Obesity
Diabetes
SIZE AT BIRTH
SMALL
NORMAL
LARGE
OUTCOMES
In the adult offspring:
Hypertension
Insulin resistance
Glucose intolerance
↑ adiposity
↓ muscle mass

Mechanisms of fetal programming

Tissue re-modelling



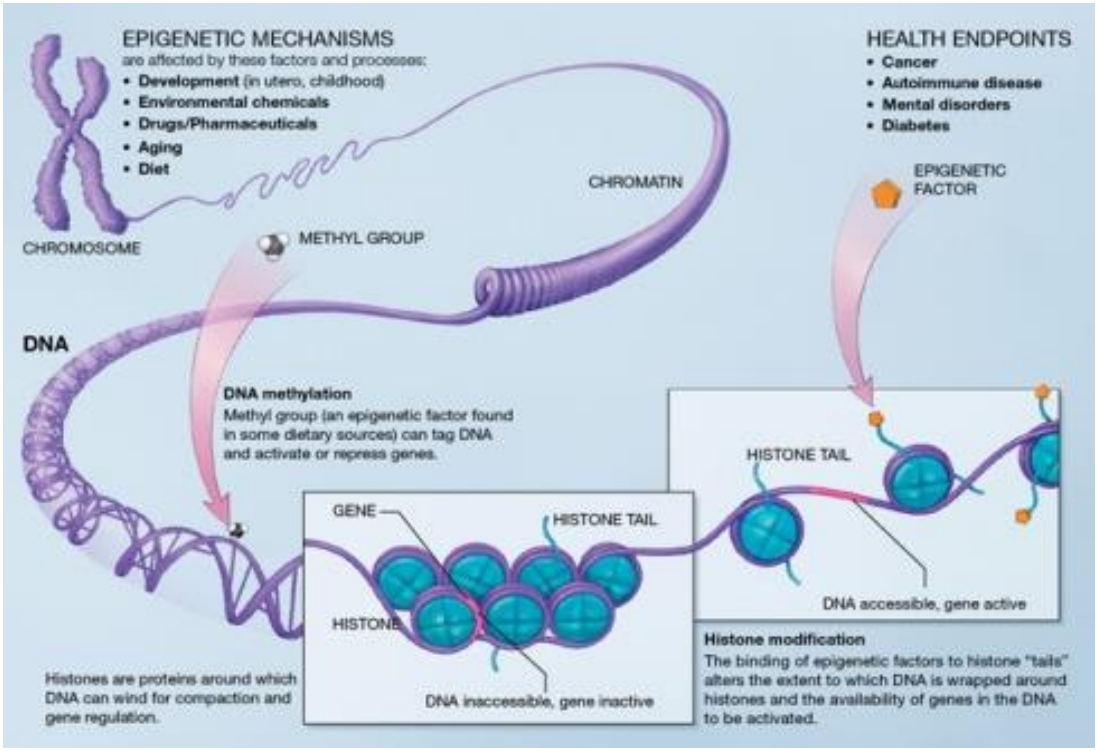
Epigenetic memory as a mechanism



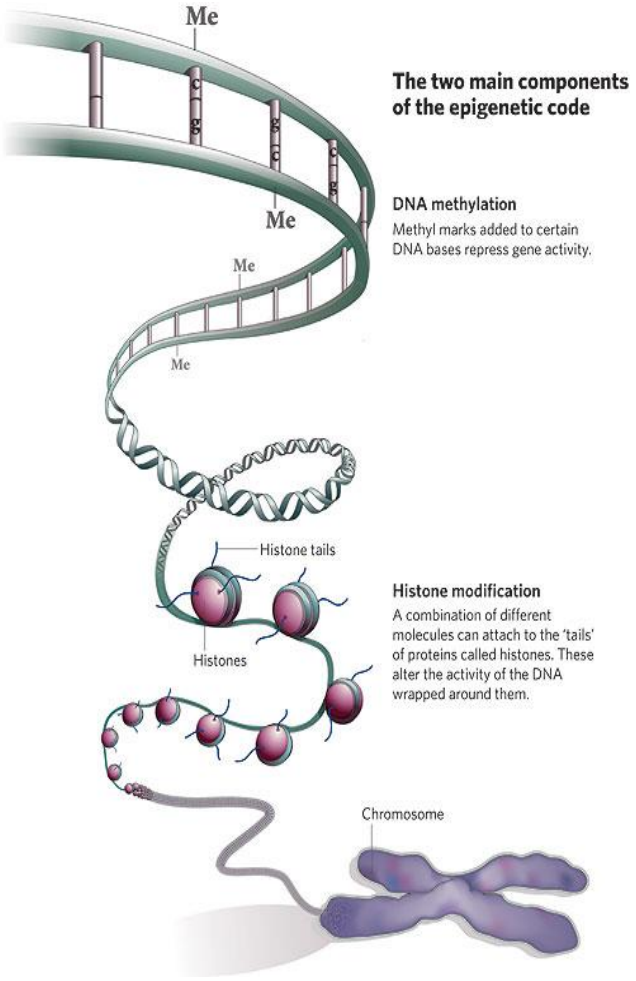
The brown mouse is genetically identical. Its mother was supplemented with methyl donor nutrients (eg folic acid) which increased DNA methylation, permanently silencing the fetal agouti gene, leading to brown coat colour and absence of adult obesity and diabetes.

The yellow mouse has low DNA methylation around the agouti gene, which gives it the yellow coat and also adult obesity and diabetes.

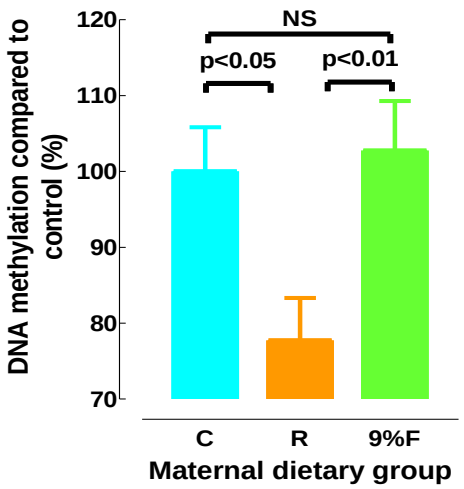
Waterland RA Mol Cell Biol 2003; 23: 5295-300

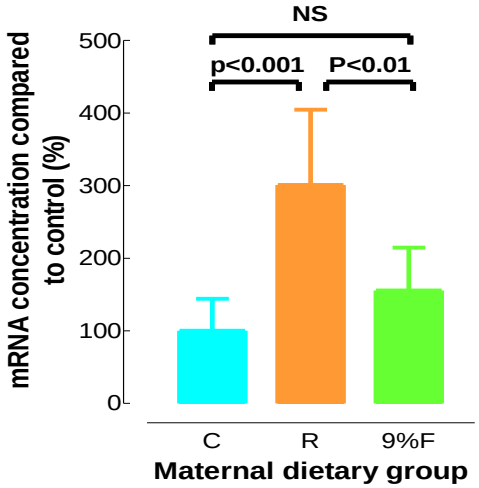


Epigenetic memory



Glucocorticoid receptor gene





A low protein diet (R) in pregnant rats reduces methylation at the glucocorticoid receptor gene in the offspring compared with controls (C). These offspring develop raised adult blood pressure. Adding folate to her diet (9%F) prevents the methylation changes and hypertension

Lillycrop KA. B J Nutr 2005;135:1382-6

Mechanisms of fetal programming

Tissue re-modelling

Nutritional deficit during critical period for nephrogenesis

↓

Reduced nephron number

↓

Increased blood pressure

↓

Accelerated nephron damaged

↓

Renin-angiotensin changes

↓

HYPERTENSION

Plasticity of the epigenome in the periconceptional period

Nutritional requirements low but nutritionally sensitive

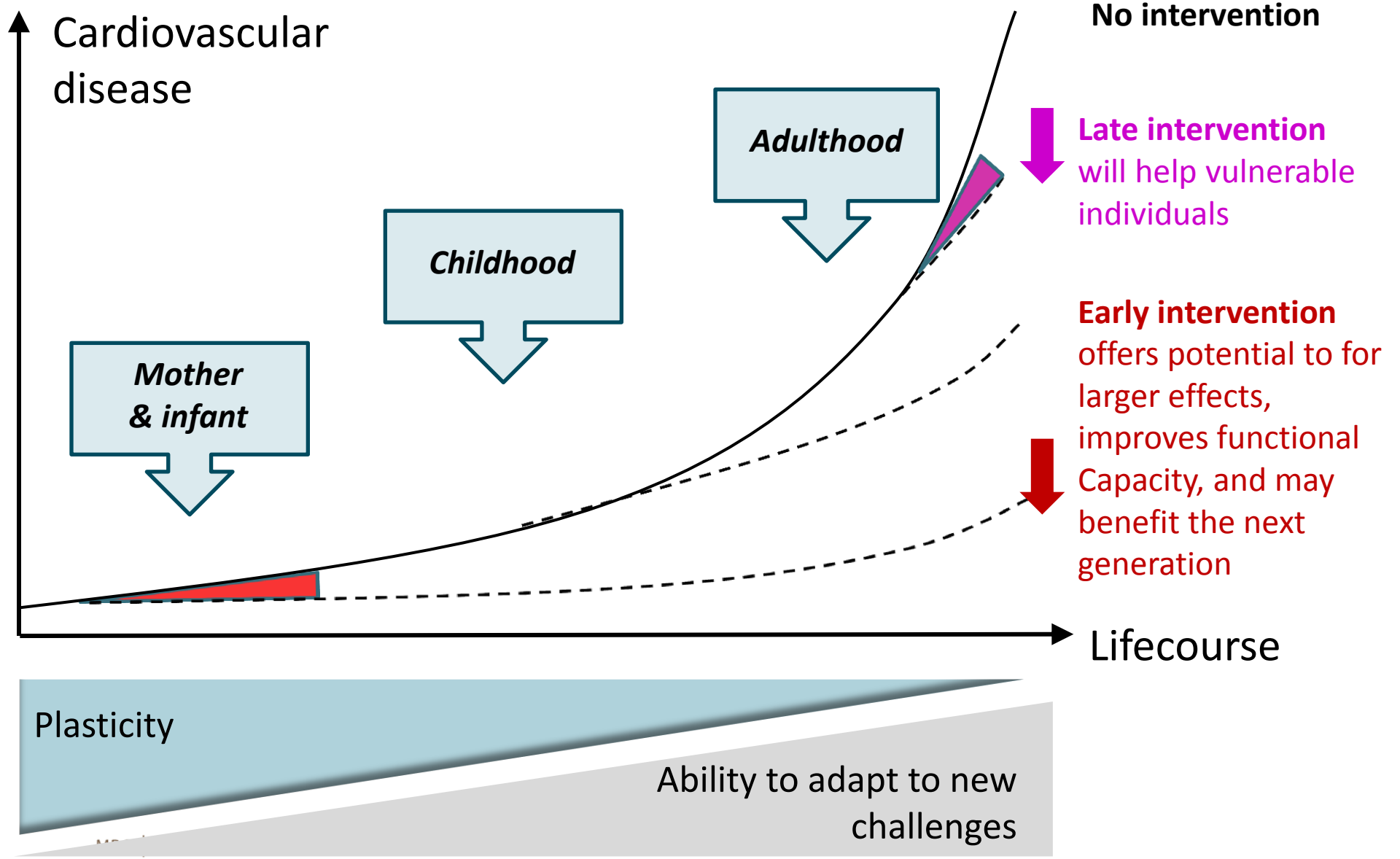
↓

Permanent hypo- or hyper-methylation of key genes eg. GCR

↓

HYPERTENSION

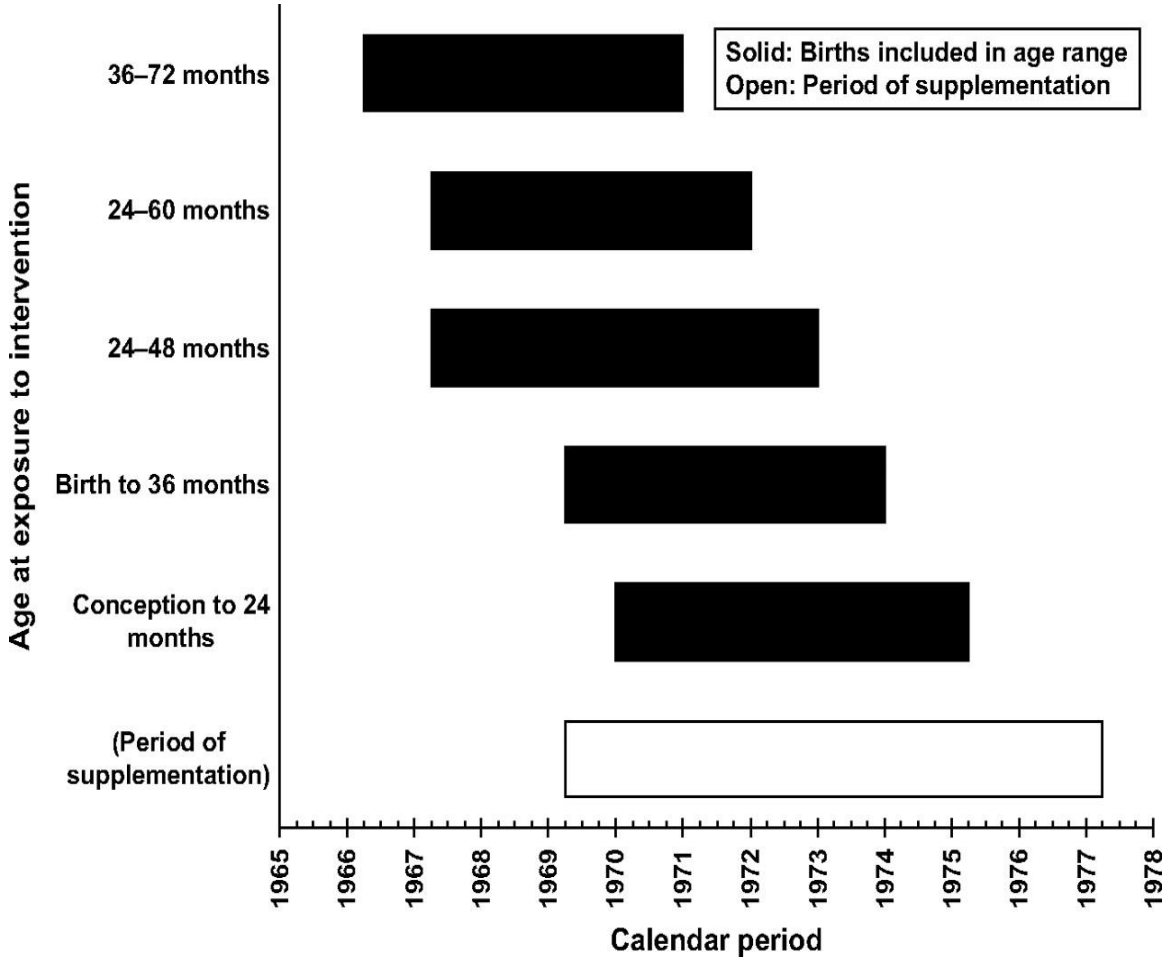
‘Primordial’ prevention of adult chronic disease



INCAP trial, Guatemala

1969-1977 Cluster randomised by village

Pregnant/lactating women and children <7 years



ATOLE

Protein 6.4 g/100ml

Energy 900 kcal/l

FRESCO

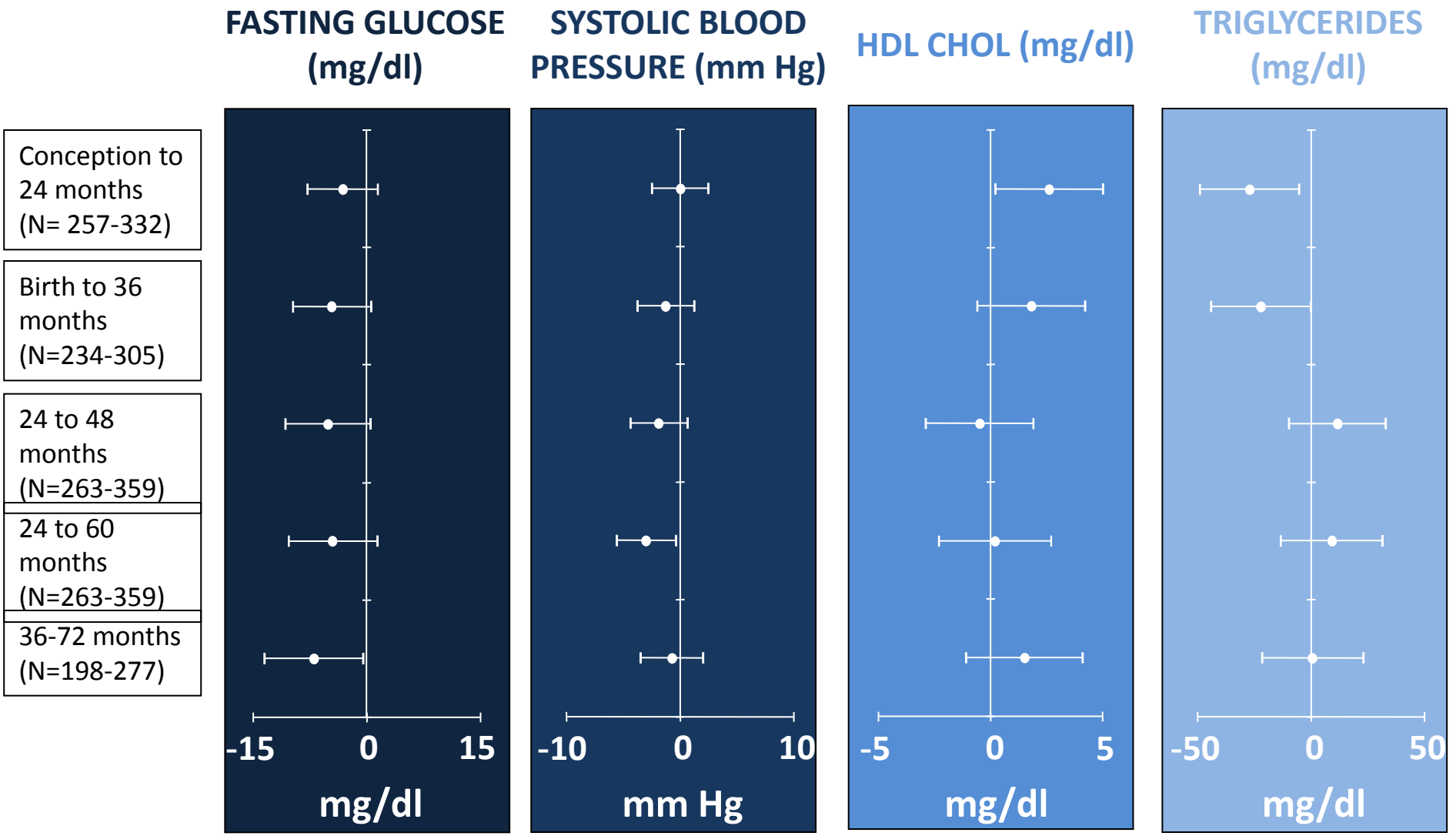
Energy 330 kcal/l

Both supplements contained multiple micronutrients

Stein AD et al. Am J Epidemiol 2006 164:1160-1170

INCAP trial, Guatemala

Effects on risk factors at 25-42 years. Atole compared with Fresco



Stein AD et al. AM J Epidemiol 2006;164:1160-1170

Long-term health outcomes in offspring of mothers who took part in randomised trials of MMN supplements, started in pregnancy, in LMICs

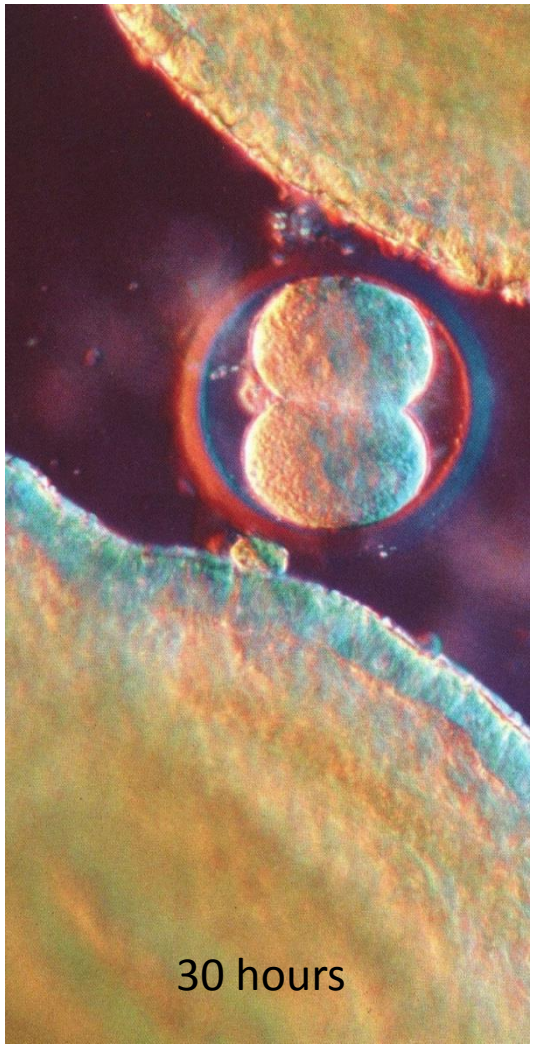
- 17 MMN trials from a 2015 Cochrane review
- Control mothers received iron and folic acid
- 9 of these trials had follow-up data in the children, aged 6 m to 8 y
- Africa (2), Asia (6), South America (1)

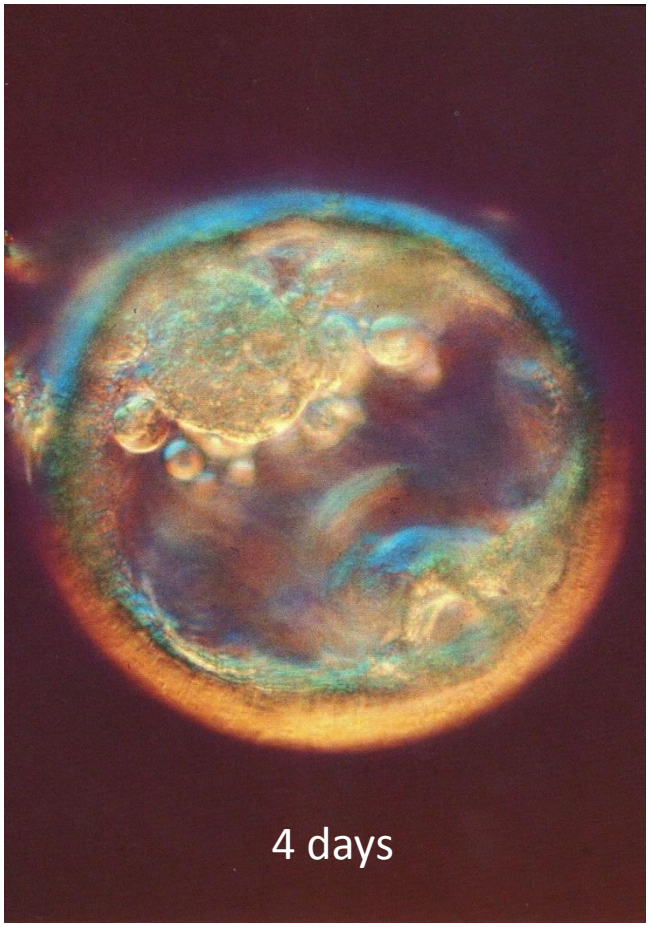
No differences in child mortality (9), WAZ/HAZ (7), blood pressure (3), cognitive function (3) or lung function (1)

- Wrong or inadequate intervention?
- Intervention started too late?
- Insufficient length of follow-up?

Devkumar D et al. BMC Medicine 2016;14:90

In animals, induction of maternal under-nutrition limited to a few days peri-conceptionally reduces fetal growth and placental size, and raises blood pressure in the adult offspring

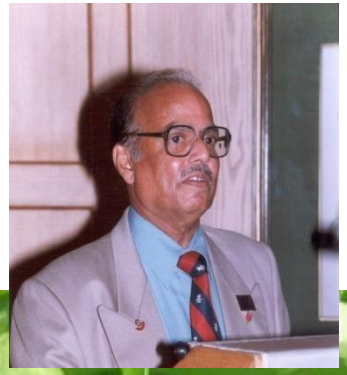




6 weeks

Fleming TP et al.
Adv Exp Med Biol
2017;1014:87-105

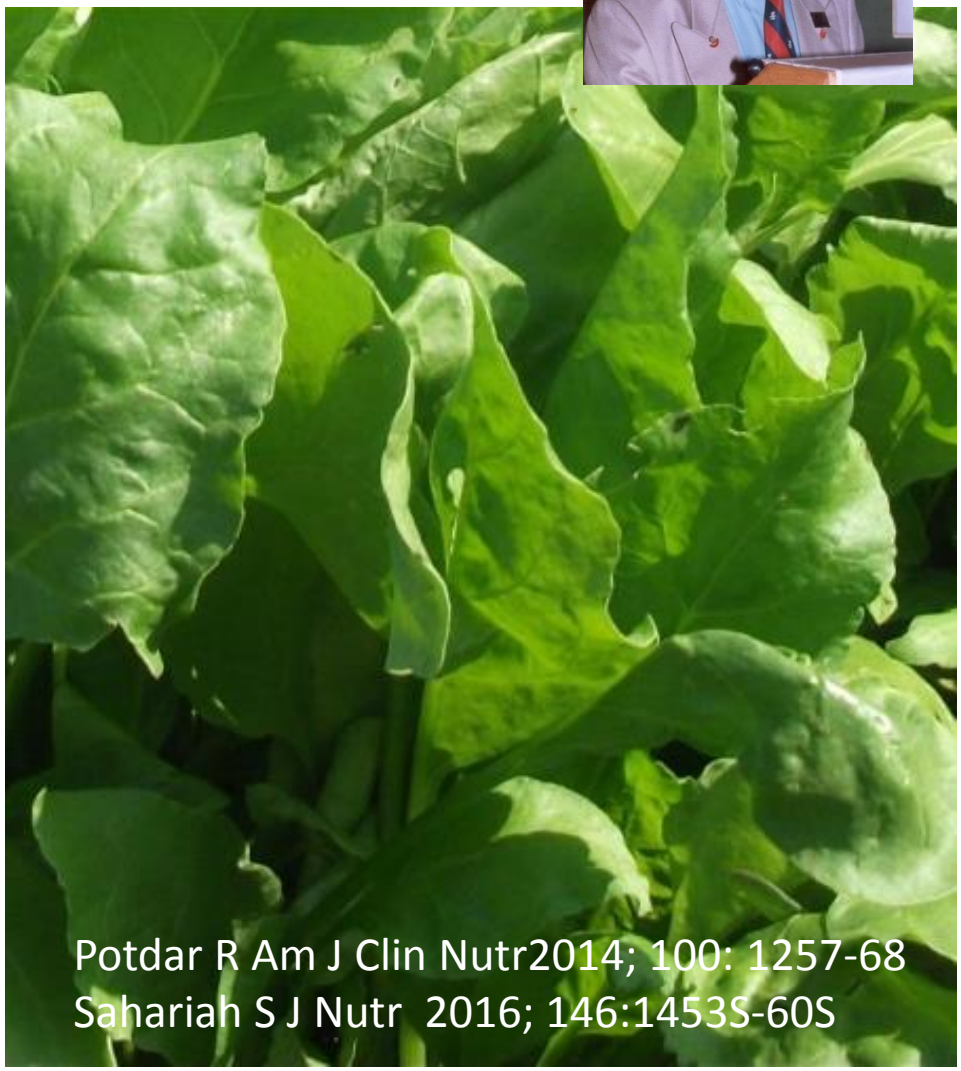
Mumbai Maternal Nutrition Project
Project SARAS ('excellent')



A randomised controlled trial (2006-2012) using green leafy vegetables, fruit and milk to improve women's diet quality for a sustained period (at least 3 months) before conception and through pregnancy.

The intervention increased birth weight and reduces gestational diabetes.

The children are being studied at 5-8 years (CVD risk markers, body composition, cognition



Potdar R Am J Clin Nutr2014; 100: 1257-68
Sahariah S J Nutr 2016; 146:1453S-60S

Pune Vitamin B12 trial
"PRIYA"

- Vitamin B12 alone 2µg/day
- Vitamin B12 + MMN
  + milk protein
- Standard care

Adolescent girls and boys

RCT
Nutrient intervention

Blood
Urine
Stool
Fat

Placenta

Cord blood
Buccal smears

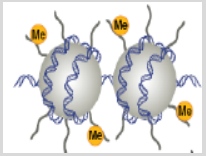
DNA

RNA

Genome

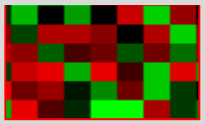
GWAS
HumanOmniExpress
Exome Beadchip

Methylome



EWAS
Illumina 450K array

Transcriptome

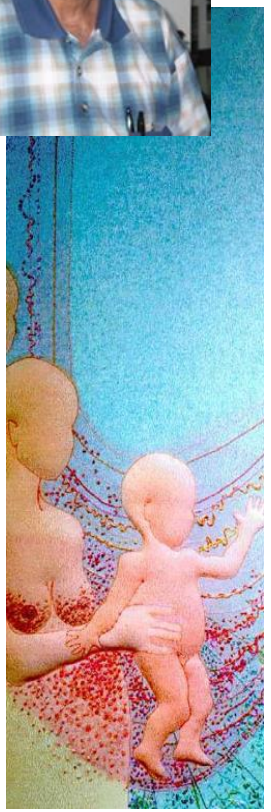


Sample collection
and storage only

Metabolome

LC- MS
1-carbon
metabolites

Data
Analysis
Integration
Mining



Mechanisms of fetal programming

Summary and messages

- Lower birthweight is associated with increased adult cardiovascular disease and type 2 diabetes
- High birthweight due to maternal diabetes or obesity is associated with increased adult obesity and type 2 diabetes
- Examples of ‘programming’ or permanent metabolic and structural changes causing vulnerability to disease
- Rapid fat gain in childhood and unhealthy adult lifestyles add to the vulnerability
- Possible mechanisms include tissue and endocrine re-modelling, and epigenetic changes
- Trials of peri-conceptional and pregnancy interventions are underway but take time to determine long-term impact
- ‘Primordial’ prevention of CVD is the objective