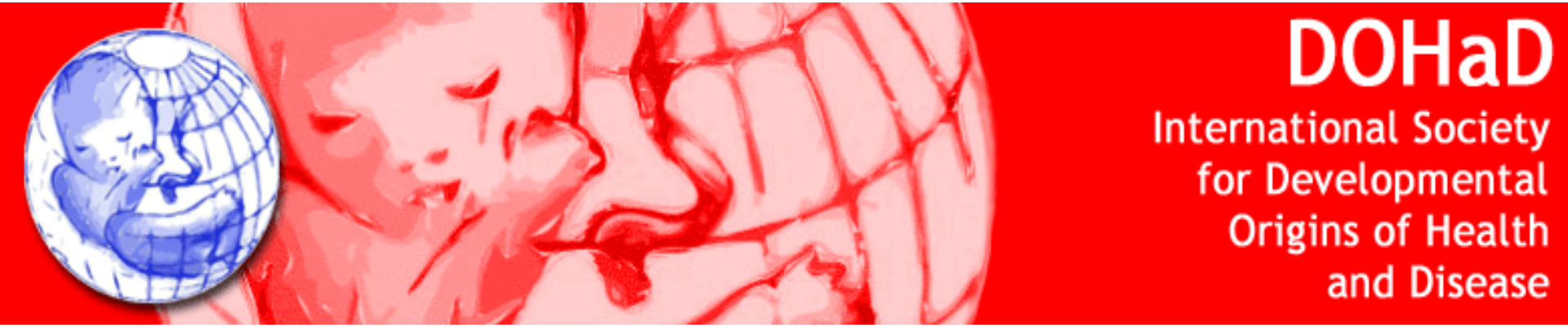
UNIVERSITY OF Southampton

Developmental Origins of Health and Disease: from concepts to interventions

Mark Hanson



DOHaD
International Society for Developmental Origins of Health and Disease

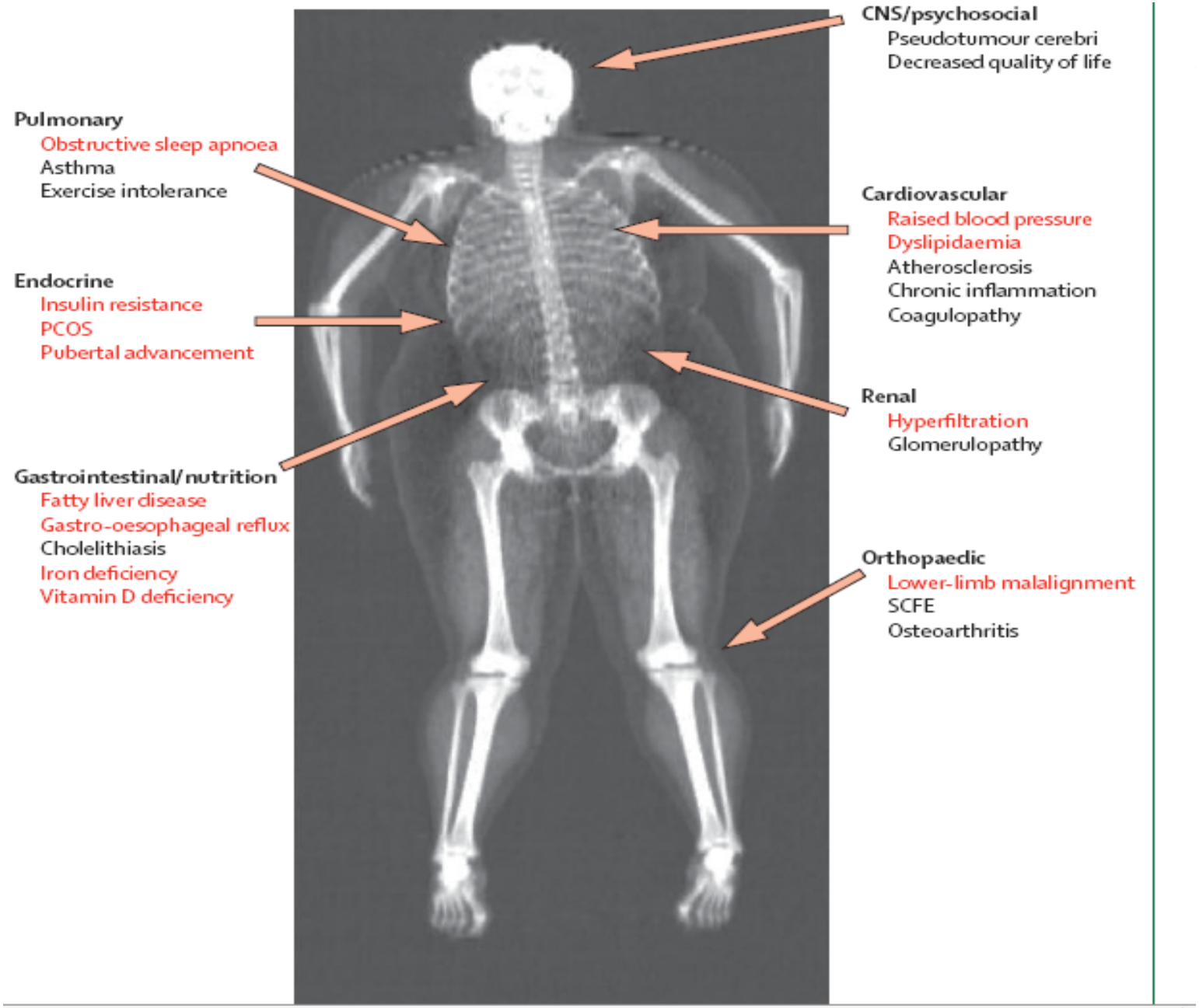
United Nations (Sept 2011)**:**
Political declaration of the High-level Meeting of the General Assembly on the Prevention & Control of Non-communicable Diseases

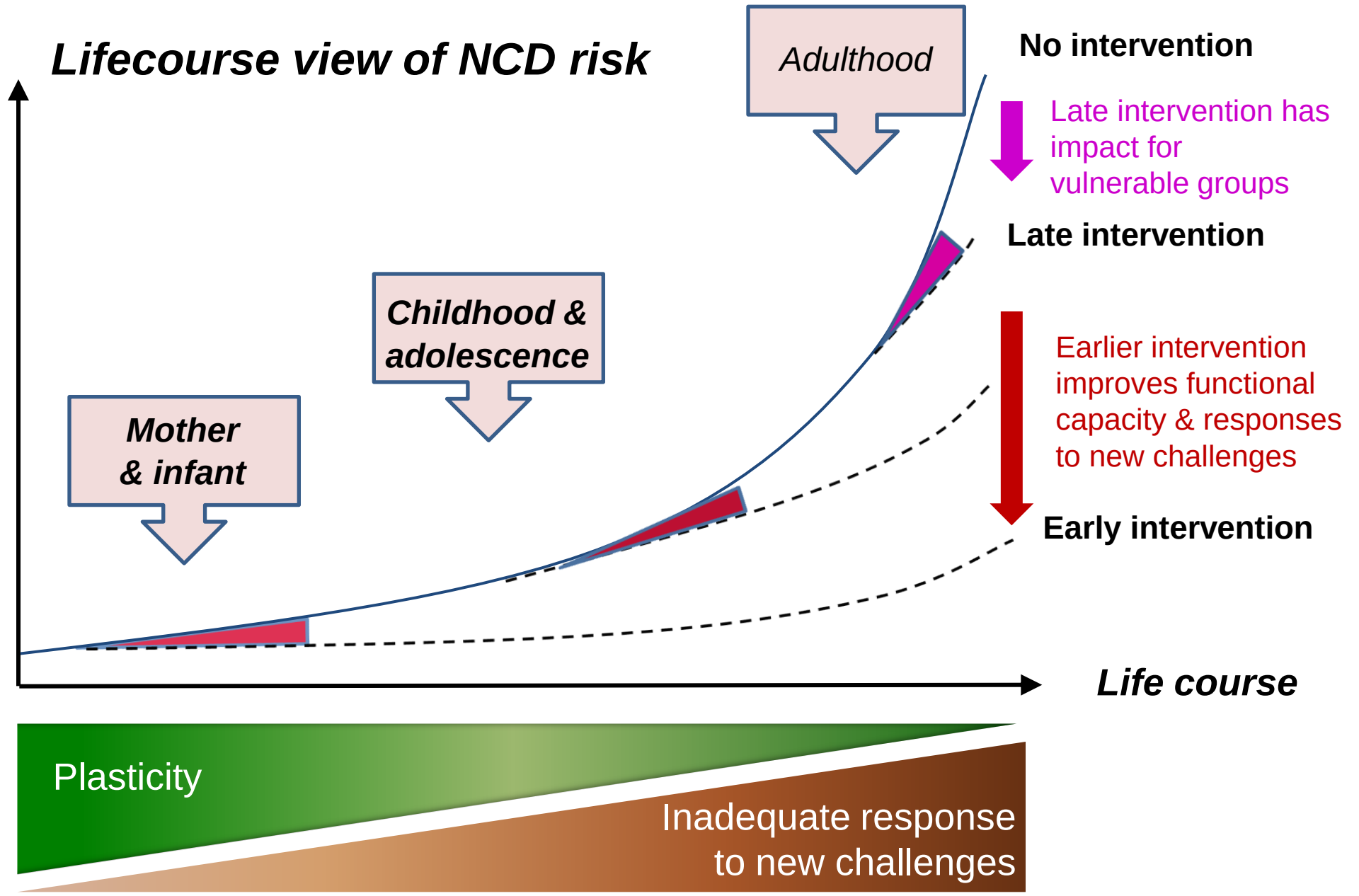
14. In 2008, an estimate 36 million of the 57 million global deaths were due to NCDs, ... and that nearly 80% of those deaths occurred in developing countries

26. {We} note also with concern that maternal and child health is inextricably linked with NCDs and their risk factors, specifically as prenatal malnutrition and low birth weight create a predisposition to obesity, high blood pressure, heart disease and diabetes later in life; and that pregnancy conditions, such as maternal obesity and gestational diabetes, are associated with similar risks in both the mother and her offspring

37. Acknowledge the contribution and important role played by all relevant stakeholders, including individuals, families, and communities, intergovernmental organizations and religious institutions, civil society, academia, media, voluntary associations, and where and as appropriate, the private sector and industry, in support of national efforts for NCD prevention and control

Consequences of childhood obesity. From Han et al (2010) Lancet 375:1737-45




Lifecourse view of NCD risk
Adulthood
No intervention
Late intervention has impact for vulnerable groups
Late intervention
Childhood & adolescence
Mother & infant
Earlier intervention improves functional capacity & responses to new challenges
Early intervention
Life course
Plasticity
Inadequate response to new challenges

Long-Term Persistence of Hormonal Adaptations to Weight Loss

Sumithran et al NEJM (2011) 365: 1597-604

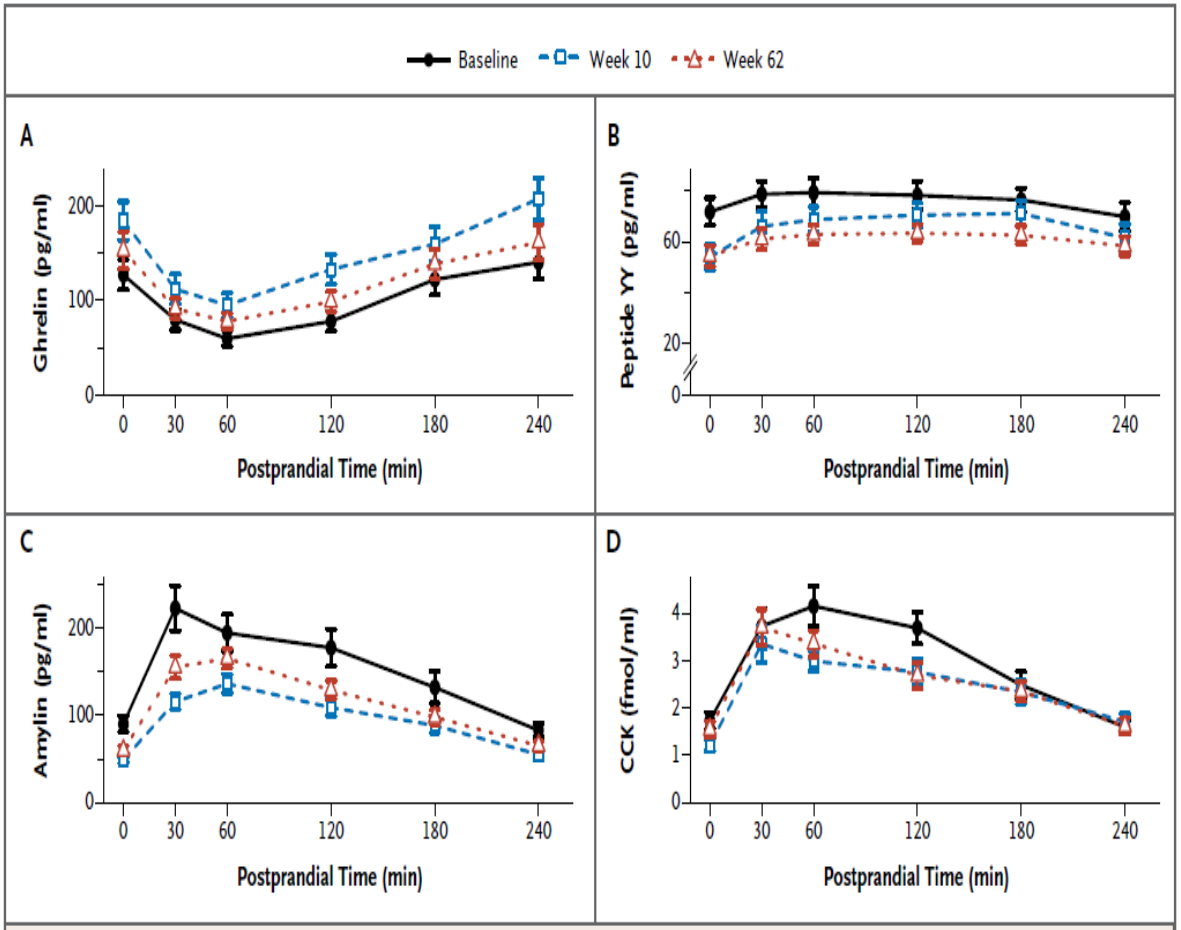


Figure 2. Mean (±SE) Fasting and Postprandial Levels of Ghrelin, Peptide YY, Amylin, and Cholecystokinin (CCK) at Baseline, 10 Weeks, and 62 Weeks.

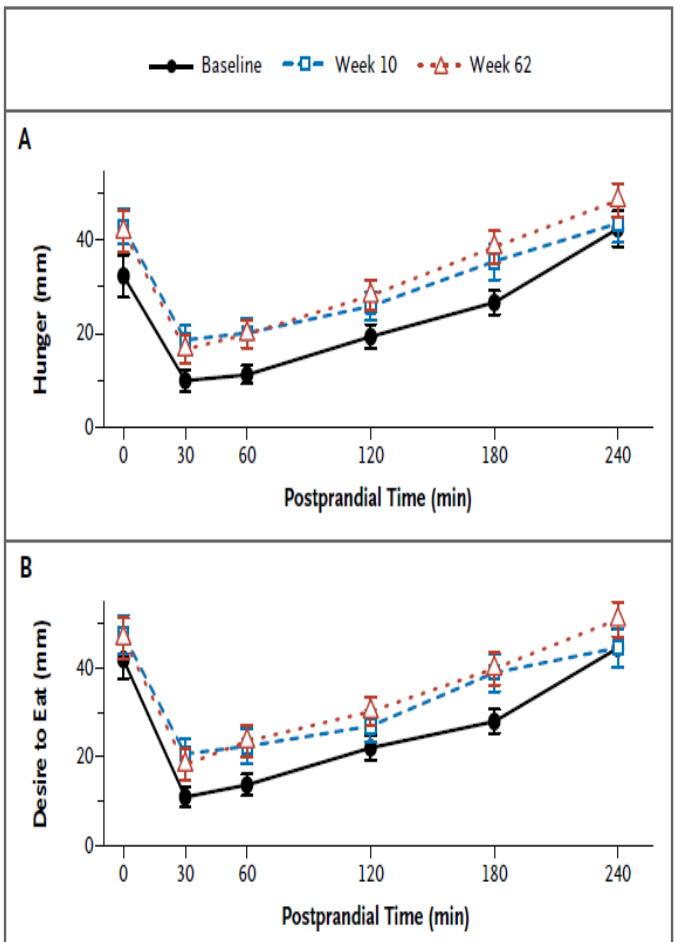
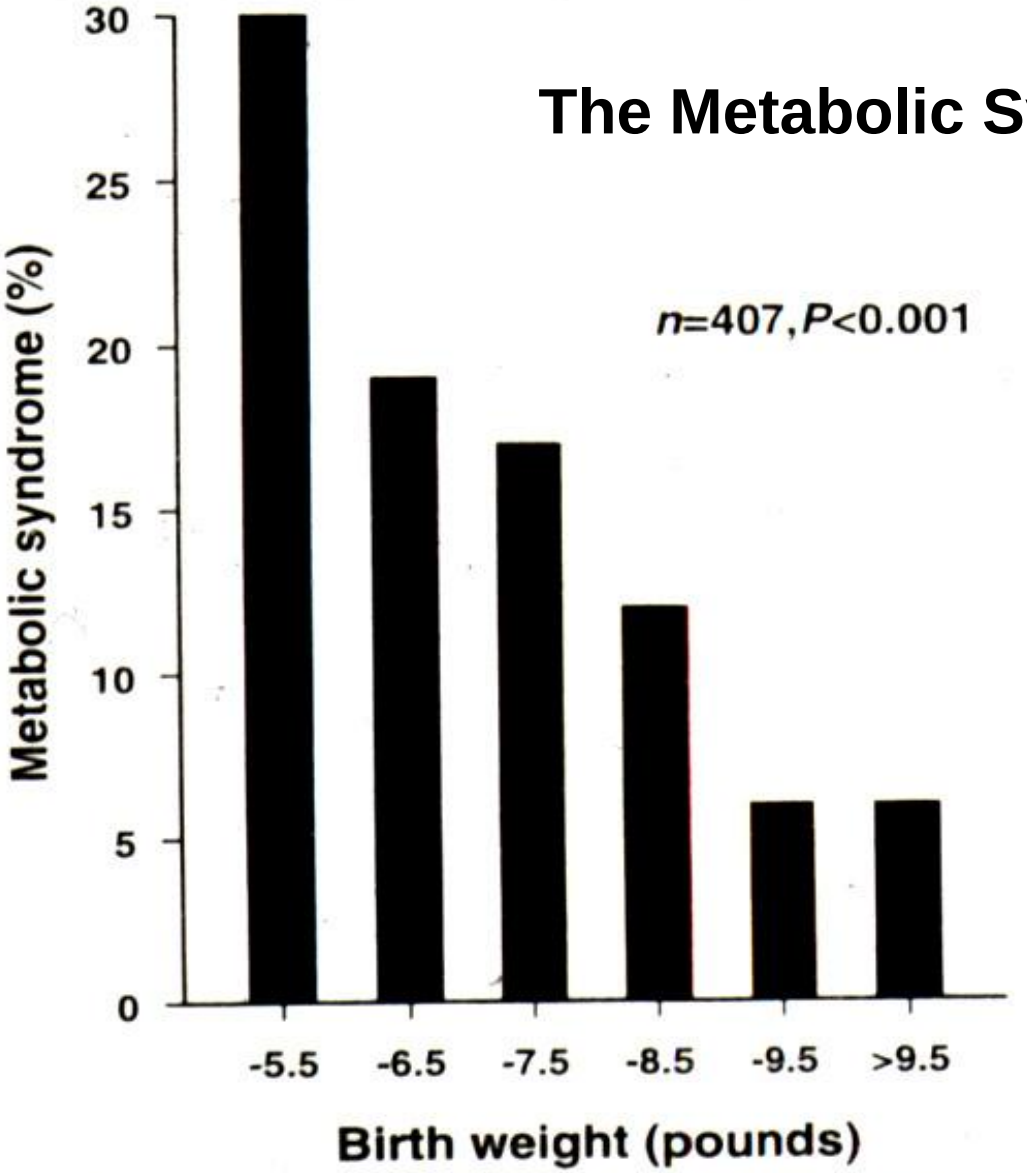


Figure 3. Mean (±SE) Fasting and Postprandial Ratings of Hunger and Desire to Eat at Baseline, 10 Weeks, and 62 Weeks.

The Metabolic Syndrome



Prevalence of the metabolic syndrome (glucose intolerance, raised blood pressure and hypertriglyceridaemia) according to birth weight in 407 men, aged 65 years, born in Hertfordshire

Thin child, thin adult
Fat child, thin adult
Fat child, fat adult
Thin child, fat adult

Children:
11.4 ± 4.0 yr
Adults:
23.1 ± 3.3 yr later

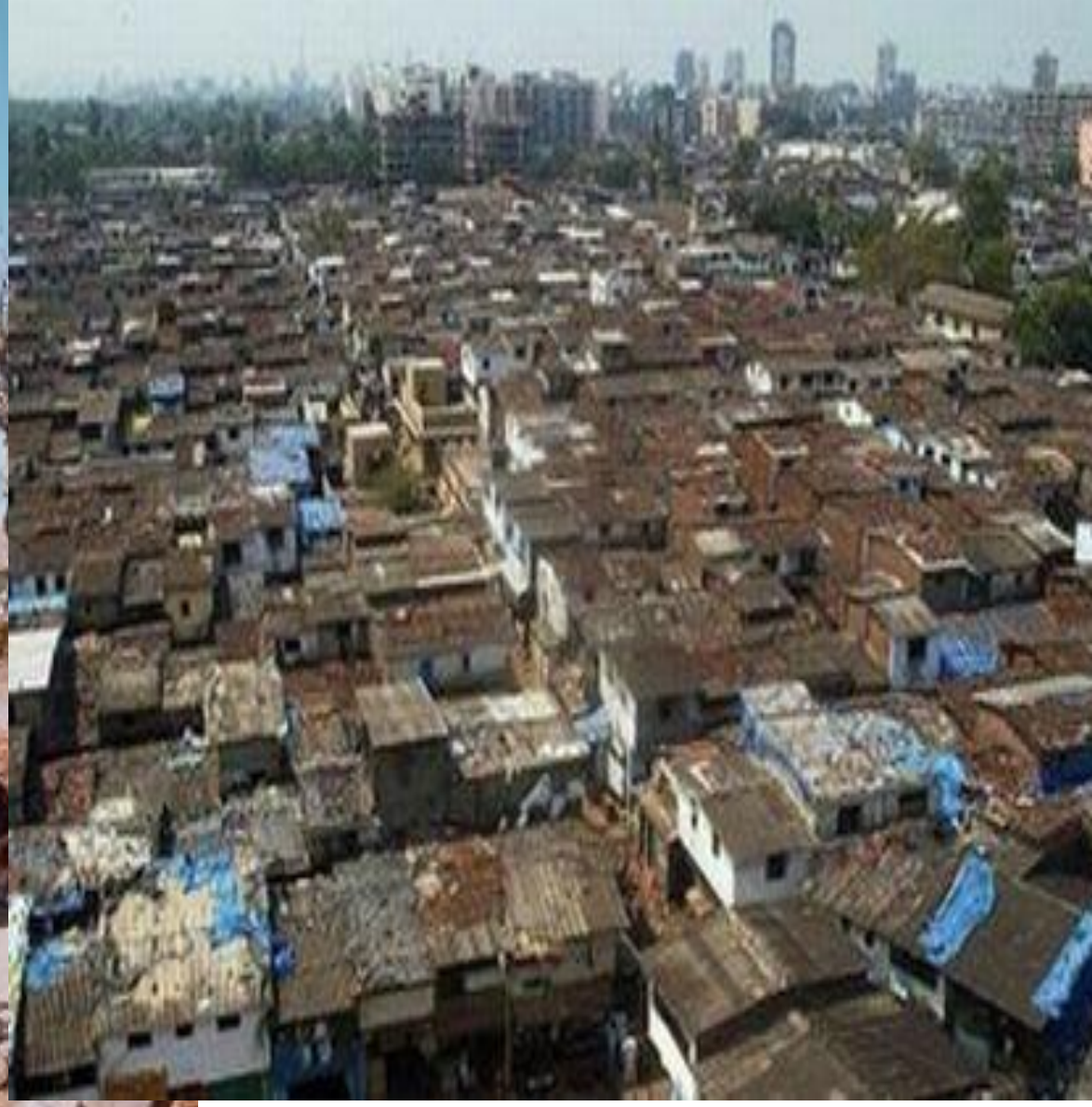
Juonala et al. (2011) NEJM 365:1876- 85

Table 3. Relative Risks of High-Risk Outcomes in Adulthood According to Adiposity Group in Childhood and Adulthood.*

Outcome and Adiposity Group	Male Subjects			Female Subjects			All Subjects		
	%	Relative Risk (95% CI)	P Value†	%	Relative Risk (95% CI)	P Value†	%	Relative Risk (95% CI)	P Value†
Type 2 diabetes									
Group I	0.5	Reference		1.3	Reference		1.0	Reference	
Group II	1.8	3.6 (0.8–16.3)	0.10	0.7	0.5 (0.1–4.0)	0.54	1.1	1.3 (0.4–4.1)	0.69
Group III	6.9	10.3 (4.7–22.7)	<0.001	7.9	3.8 (2.1–6.8)	<0.001	7.4	5.4 (3.4–8.5)	<0.001
Group IV	4.6	7.5 (3.5–16.1)	<0.001	6.9	3.5 (2.1–5.9)	<0.001	5.8	4.5 (2.9–6.8)	<0.001
Hypertension									
Group I	15.3	Reference		6.9	Reference		10.8	Reference	
Group II	16.0	1.1 (0.7–1.8)	0.61	3.2	0.6 (0.2–1.4)	0.25	8.8	0.9 (0.6–1.4)	0.80
Group III	37.0	2.5 (2.0–3.2)	<0.001	19.6	3.2 (2.3–4.4)	<0.001	28.5	2.7 (2.2–3.3)	<0.001
Group IV	30.0	1.8 (1.4–2.2)	<0.001	19.6	2.6 (2.0–3.4)	<0.001	23.6	2.1 (1.7–2.4)	<0.001
High-risk LDL cholesterol									
Group I	12.7	Reference		5.9	Reference		9.1	Reference	
Group II	13.6	1.1 (0.7–1.9)	0.61	4.6	0.9 (0.4–1.9)	0.79	8.5	1.1 (0.7–1.6)	0.81
Group III	19.0	1.5 (1.1–2.0)	0.02	16.5	2.7 (1.8–3.9)	<0.001	17.8	1.8 (1.4–2.3)	<0.001
Group IV	22.3	1.7 (1.3–2.2)	<0.001	8.2	1.3 (0.9–1.8)	0.25	14.7	1.5 (1.2–1.9)	<0.001
High-risk HDL cholesterol									
Group I	23.9	Reference		7.2	Reference		15.0	Reference	
Group II	21.9	0.9 (0.6–1.3)	0.58	8.5	1.1 (0.6–2.0)	0.64	14.3	1.0 (0.7–1.3)	0.77
Group III	47.2	1.7 (1.4–2.1)	<0.001	30.5	3.3 (2.4–4.3)	<0.001	39.1	2.1 (1.8–2.5)	<0.001
Group IV	51.7	2.0 (1.7–2.3)	<0.001	25.7	3.0 (2.3–3.8)	<0.001	38.1	2.2 (1.9–2.6)	<0.001
High-risk triglycerides									
Group I	11.0	Reference		4.2	Reference		7.4	Reference	
Group II	5.9	0.6 (0.3–1.2)	0.13	3.9	1.0 (0.4–2.3)	0.99	4.8	0.7 (0.4–1.2)	0.21
Group III	34.0	3.0 (2.4–3.9)	<0.001	12.4	2.9 (1.9–4.4)	<0.001	23.4	3.0 (2.4–3.8)	<0.001
Group IV	35.7	3.2 (2.6–3.9)	<0.001	15.0	3.2 (2.3–4.4)	<0.001	25.0	3.2 (2.7–3.8)	<0.001
High-risk carotid-artery intima–media thickness									
Group I	12.5	Reference		12.7	Reference		12.6	Reference	
Group II	15.2	1.2 (0.7–1.9)	0.49	8.8	0.7 (0.4–1.2)	0.16	11.7	0.9 (0.6–1.3)	0.54
Group III	18.1	1.5 (1.1–2.2)	0.01	22.5	1.9 (1.4–2.6)	<0.001	20.2	1.7 (1.4–2.2)	0.002
Group IV	17.5	1.5 (1.1–1.9)	0.007	17.9	1.6 (1.2–2.0)	<0.001	17.7	1.5 (1.3–1.8)	0.009

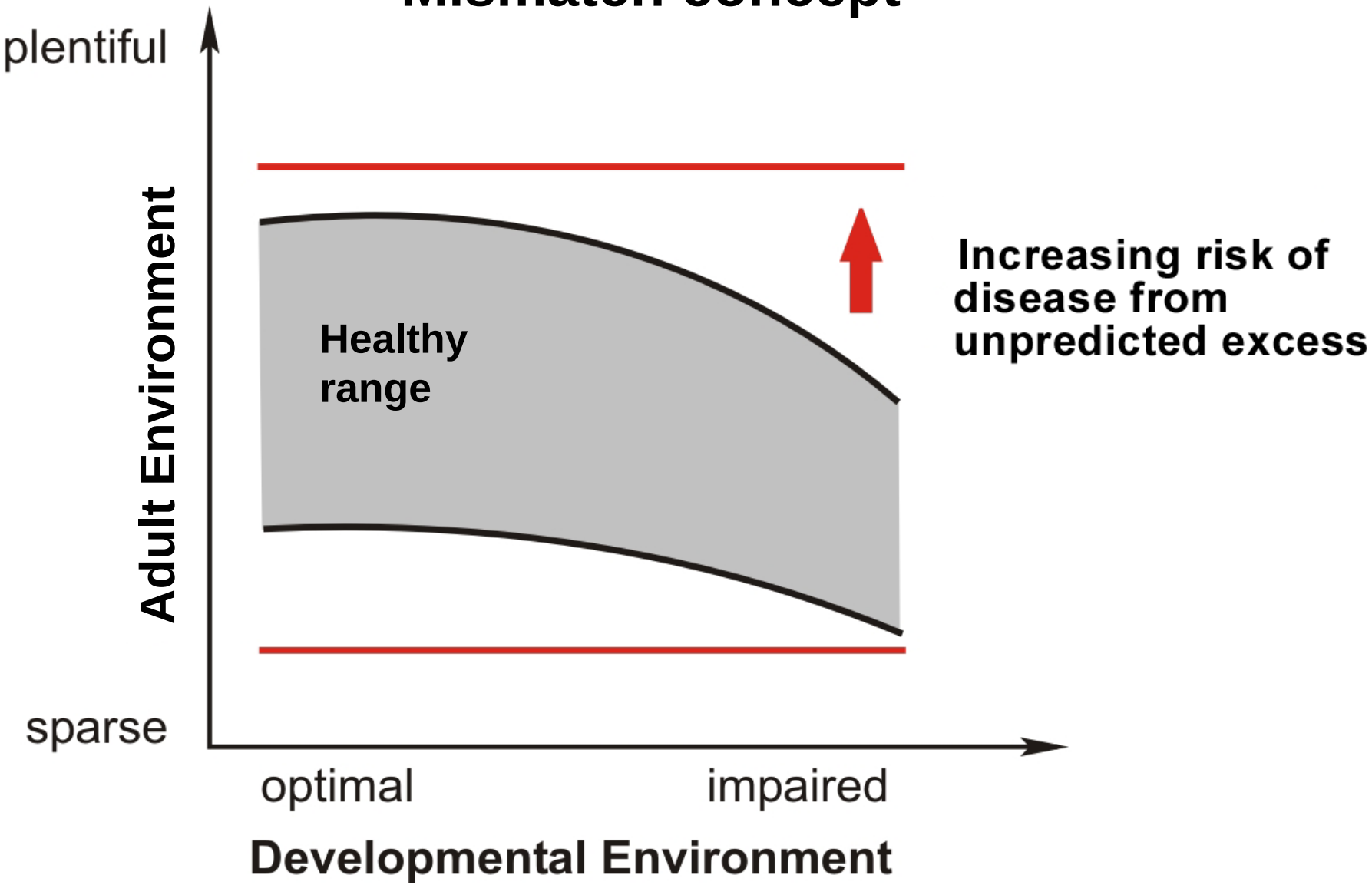
* Data are pooled from four large studies of cardiovascular risk factors — the Bogalusa Heart Study, the Muscatine Study, the Childhood Determinants of Adult Health study, and the Cardiovascular Risk in Young Finns Study. The analyses were adjusted for age, sex, height, length of follow-up, and cohort. The adiposity groups were as follows: group I (4742 subjects) included subjects with a normal BMI in childhood who were nonobese as adults; group II (274 subjects), those who were overweight or obese in childhood but nonobese as adults; group III (500 subjects), those who were overweight or obese in childhood and obese as adults; and group IV (812 subjects), those with a normal BMI in childhood who were obese as adults.

† P values are for the comparison with group I (reference).



“Mismatch”

Mismatch concept

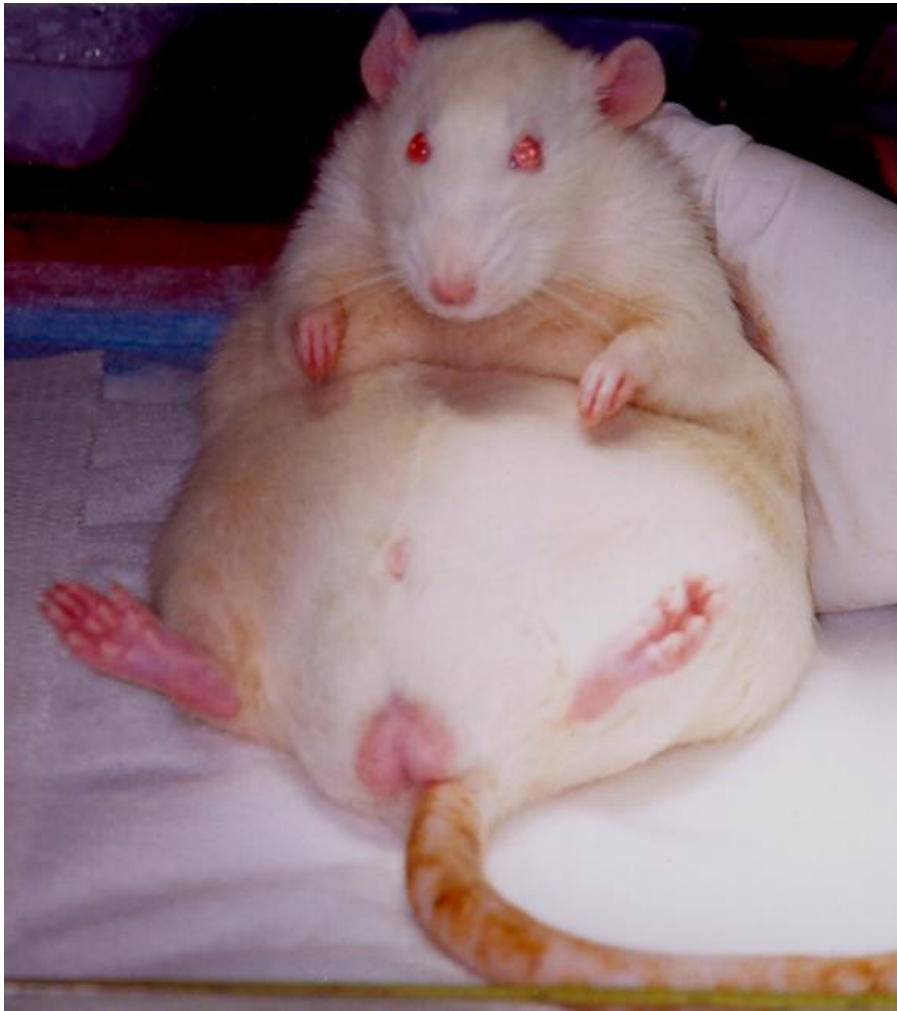


Modified from Gluckman PD, Hanson MA (2004) *Science* 305 (5691):1733-6

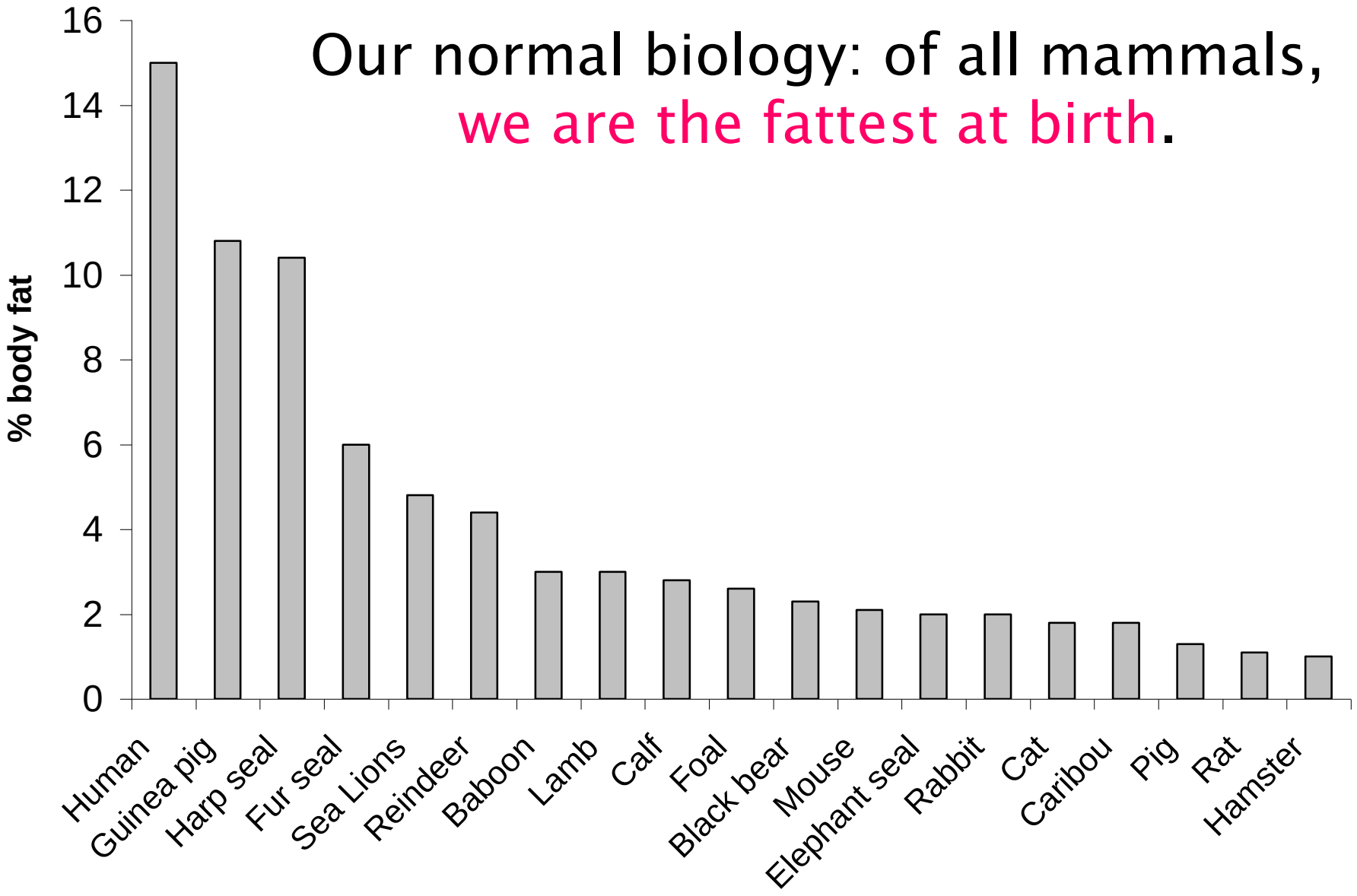
Animal models

Rat – mother fed an unbalanced diet (protein/ carbohydrate/ fat) during pregnancy, and offspring fed an adequate or excessive diet ("mismatched") This produces a range of health problems in adulthood, similar to human disease

- Obesity
- Reduced muscle mass
- Reduced bone density
- Fatty liver
- High blood pressure/ vascular dysfunction
- Insulin and Leptin resistance
- Altered appetite/ hyperphagia/ fatty food preference
- Altered stress hormones/ anxiety
- Reduced learning
- Earlier puberty



Our normal biology: of all mammals, we are the fattest at birth.



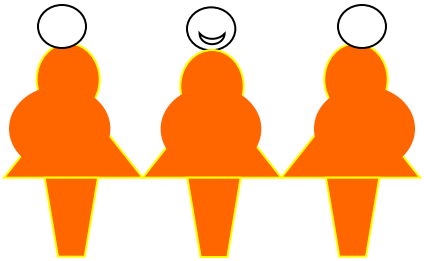
The Importance of Prospective studies – e.g. Southampton Women's Survey (SWS)

Population of 12,500 non-pregnant Southampton women aged 20-34 years interviewed about diet, physical activity, social circumstances & lifestyle; body fatness measured; DNA & blood samples taken.

3150 pregnancies studied

Ultrasounds at 11, 19, 34 wks

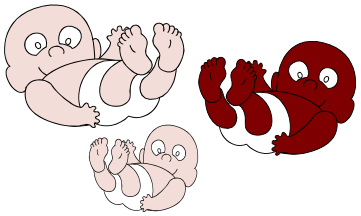
Interviews at 11 & 34 weeks



Maternal grandparents' DNA

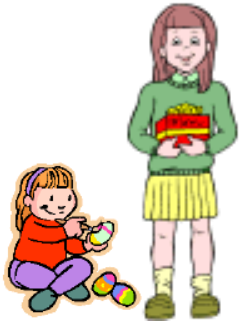
Maternal blood samples

Paternal DNA & blood



Neonatal size & thinness/fatness; cord blood; placental samples

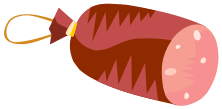
Offspring home visits at 6, 12, 24 & 36 months. Clinic/home visits at 4, 6 & 8 years

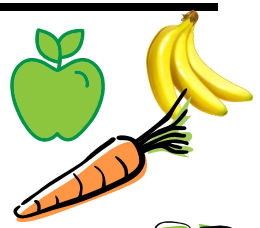


Median times per week food is consumed in the least and most ‘prudent’ diet quarters

Food	Least prudent	Most prudent
Sugar	21	0
White bread	14	3
Red meat and processed meat	7	2
Crisps and confectionery	10	4
Fruit and fruit juice	7	18
Non-salad vegetables	9	17
Salad vegetables	3	11

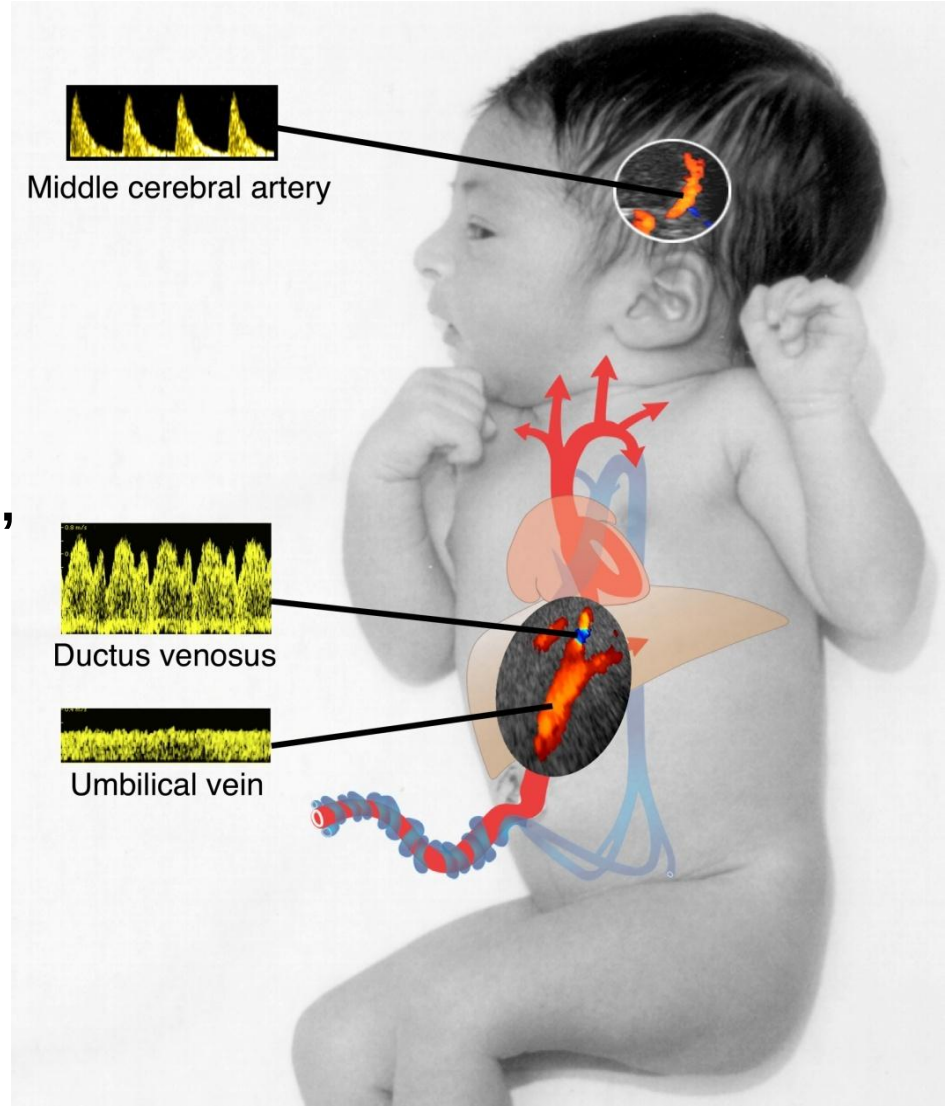







What processes influence fetal fat deposition?

Fetal liver blood flow has long-term implications for liver metabolism, growth factor production and fat deposition

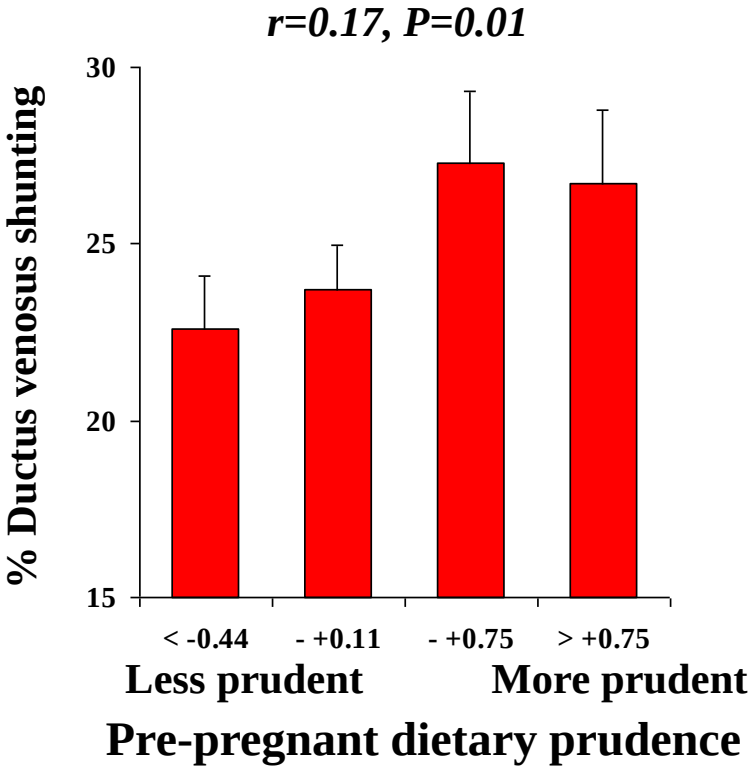


Haugen et al (2005) Circulation Research 96(1): 12-4

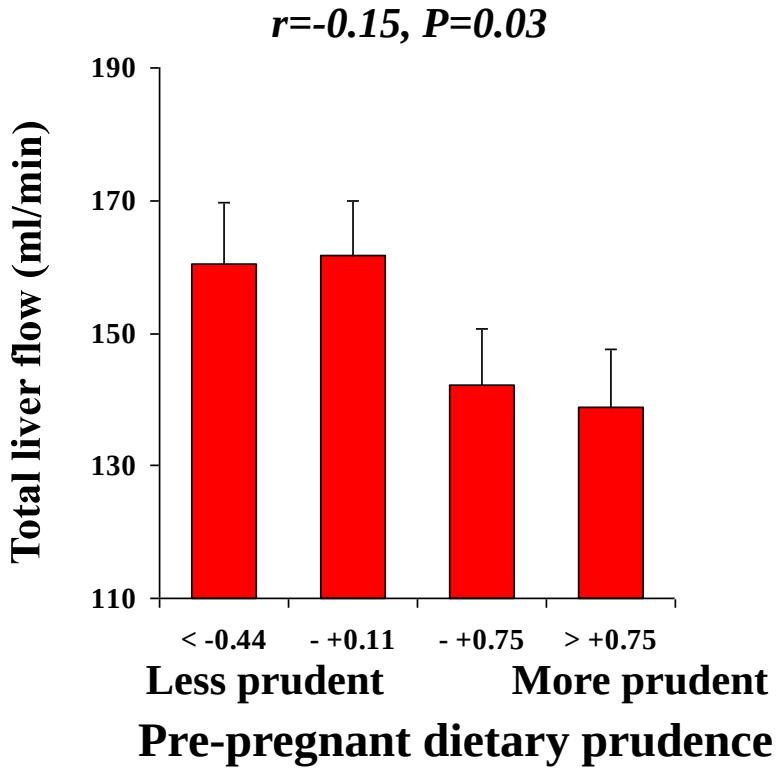
Mother's diet before pregnancy

"less prudent diet" <u>low</u> fruit / vegetables, <u>high</u> red meat / white bread / sugar / crisps

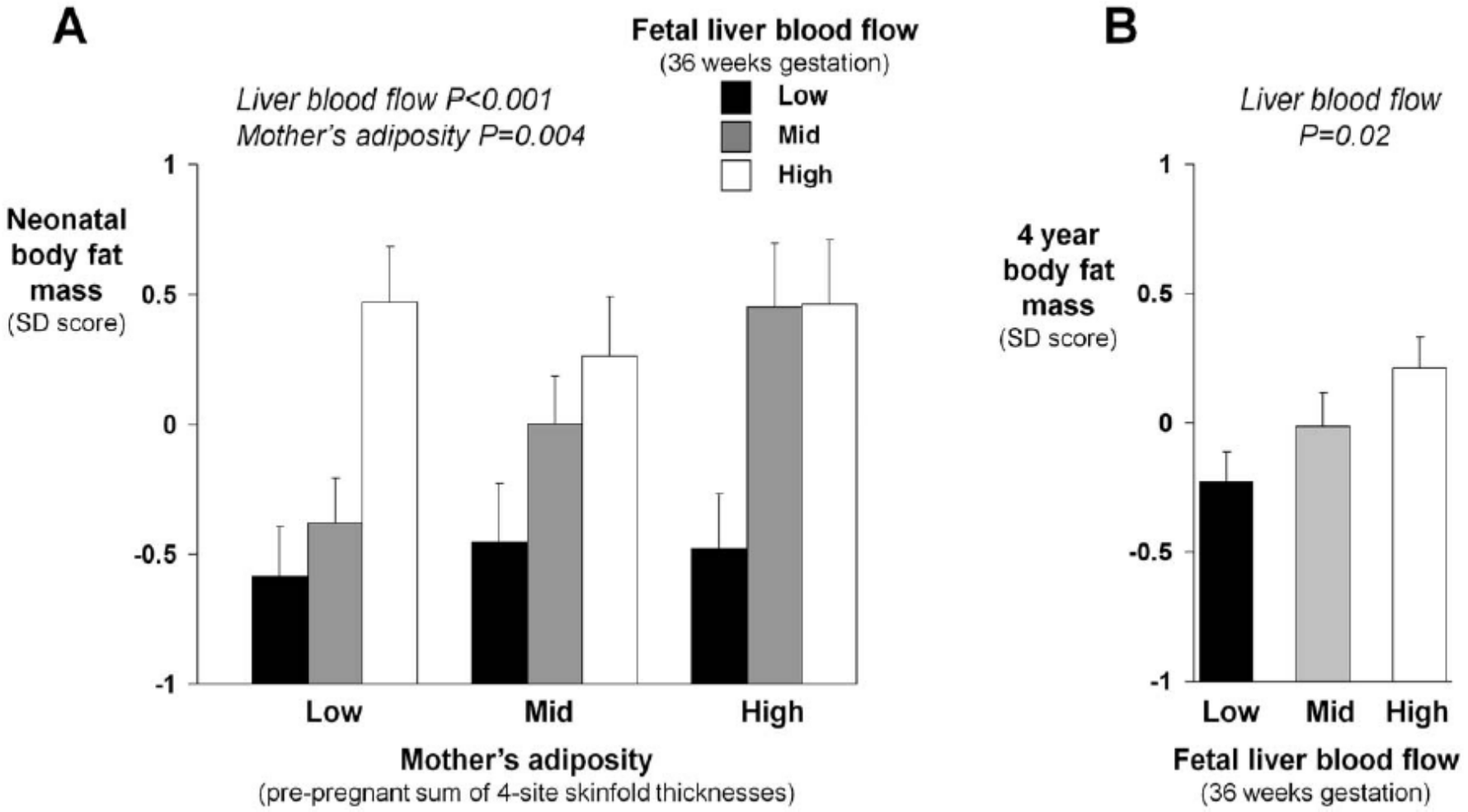
Ductus venosus shunting



Total liver flow

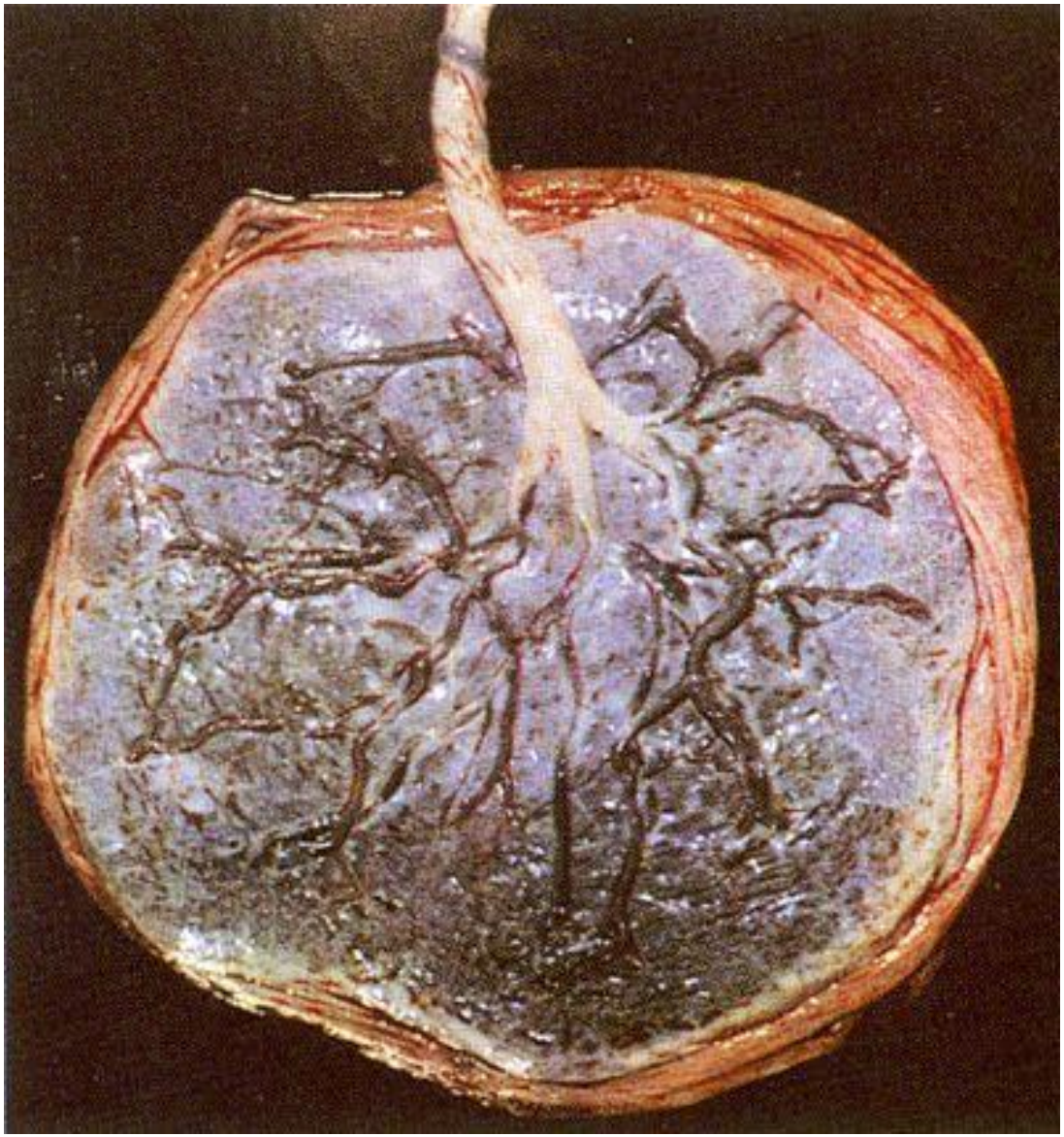


Haugen et al (2005) Circulation Research 96(1): 12-14

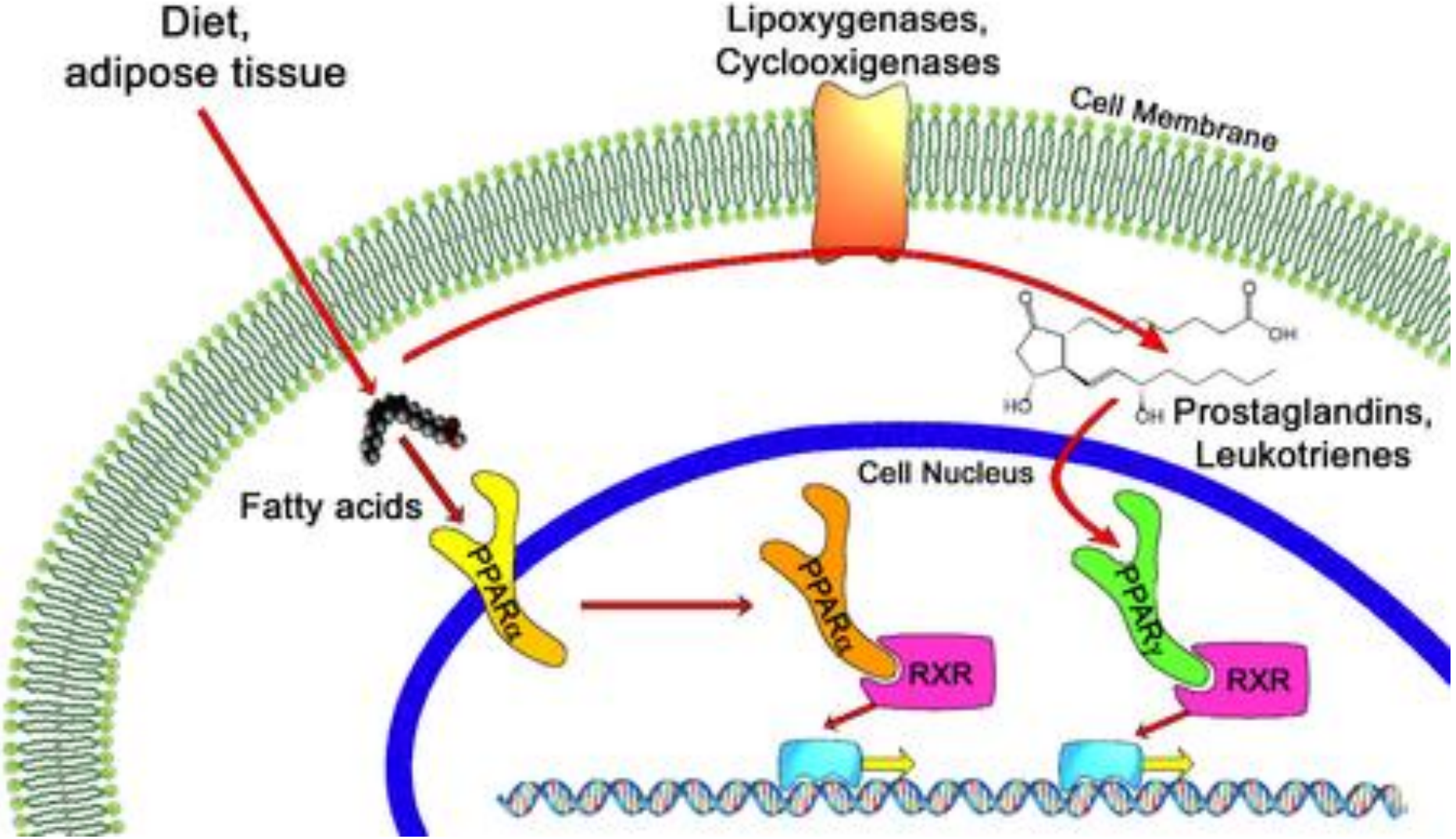


Godfrey KM et al PLoSOne August 2012 | Volume 7 | Issue 8 | e41759

Which tissues are available for epigenetic analysis?



Candidate gene pathways involved

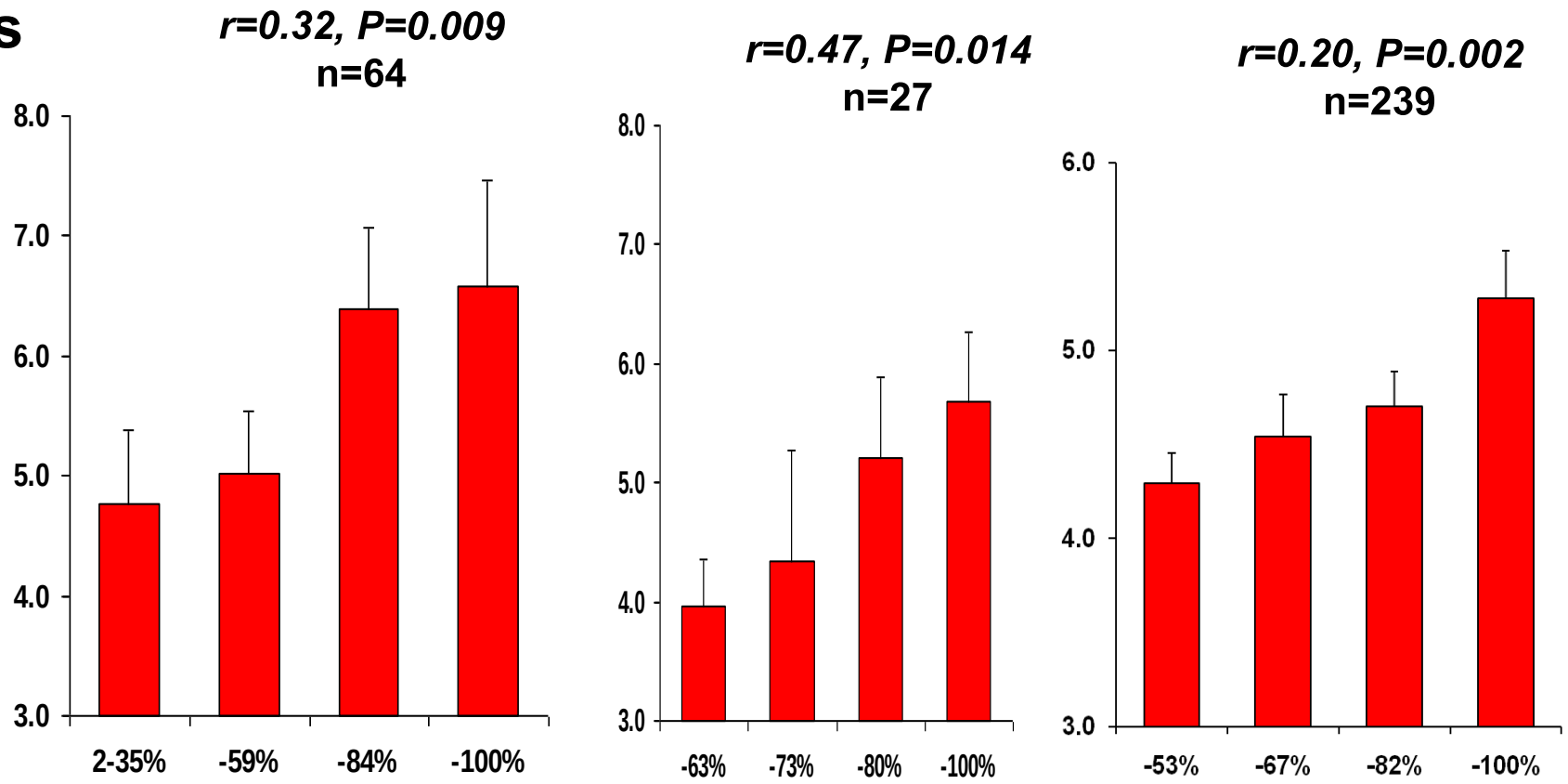


Epigenetic state at birth predicts body composition in childhood

Child's fat mass (kg)

PAH study children aged 9 years

SWS children aged 6 years



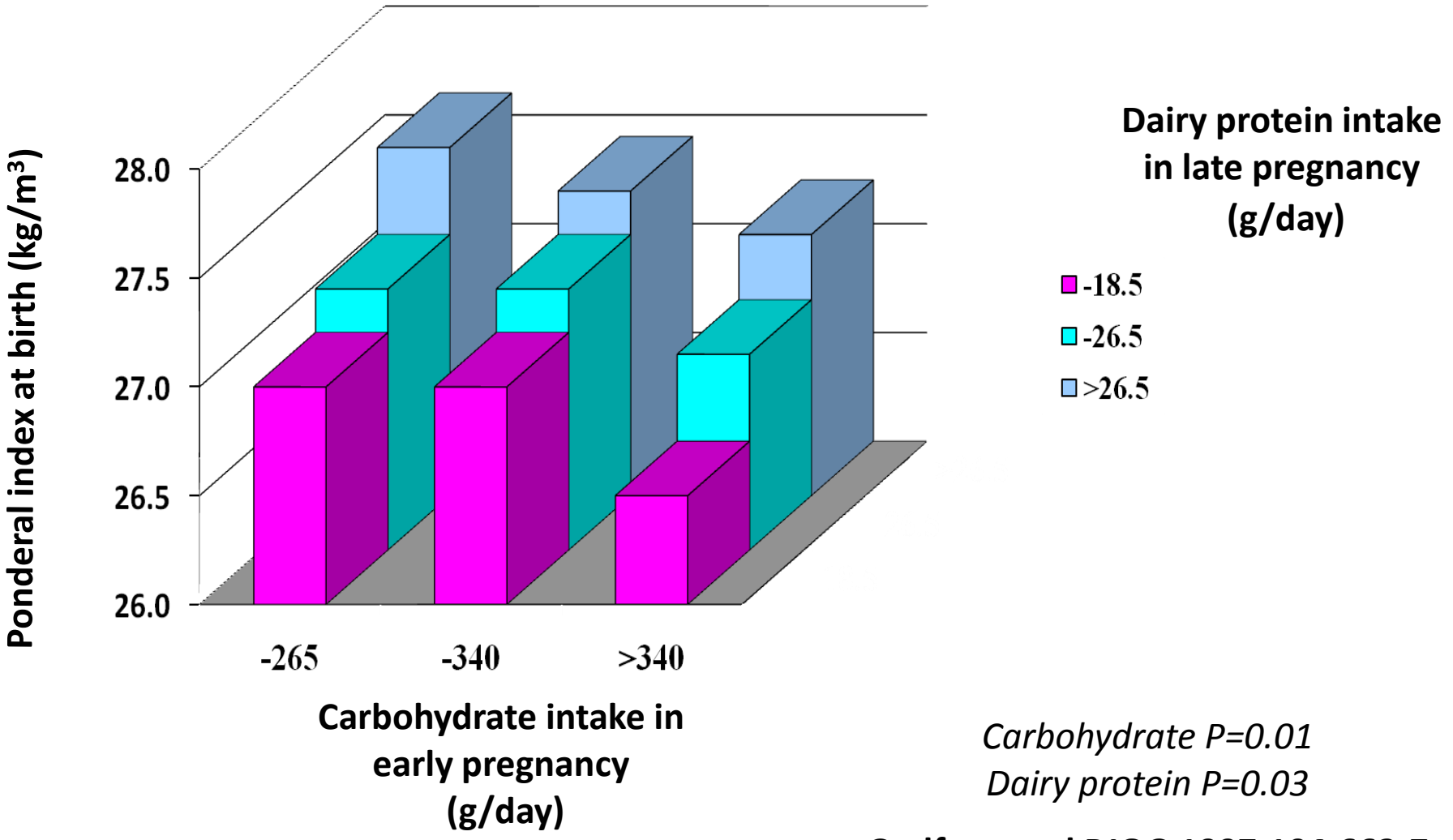
Degree of epigenetic change in one CpG in RXRa gene

Godfrey et al 2011 (*Diabetes* 60: 1528- 1534)

Values are means + SEM

Diet in pregnancy & ponderal index at birth

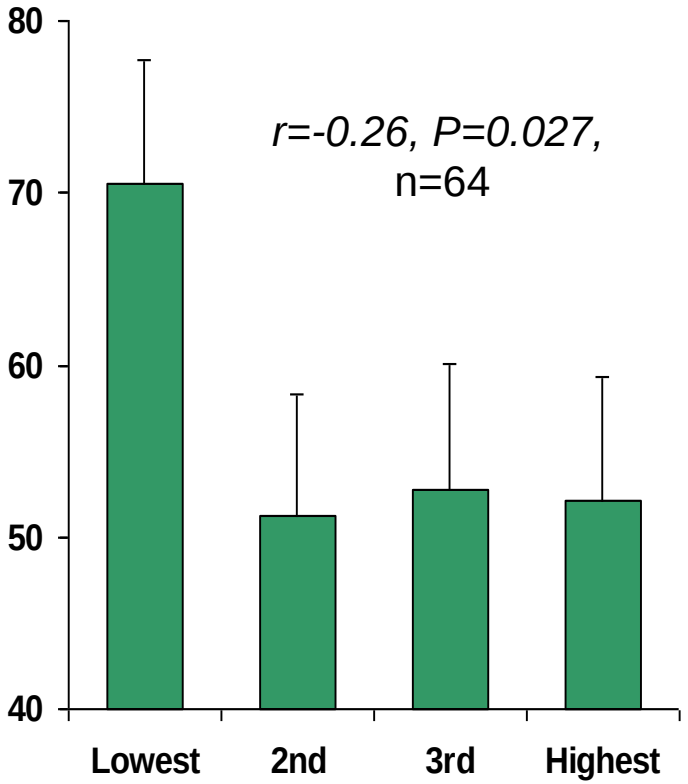
538 term Southampton pregnancies



Carbohydrate P=0.01
Dairy protein P=0.03

Godfrey et al BJOG 1997;104:663-7

Low maternal carbohydrate intake in early pregnancy associated with higher umbilical cord RXRA gene promoter methylation



Epigenetic change in RXRa gene

Maternal carbohydrate intake in early pregnancy (quartiles)

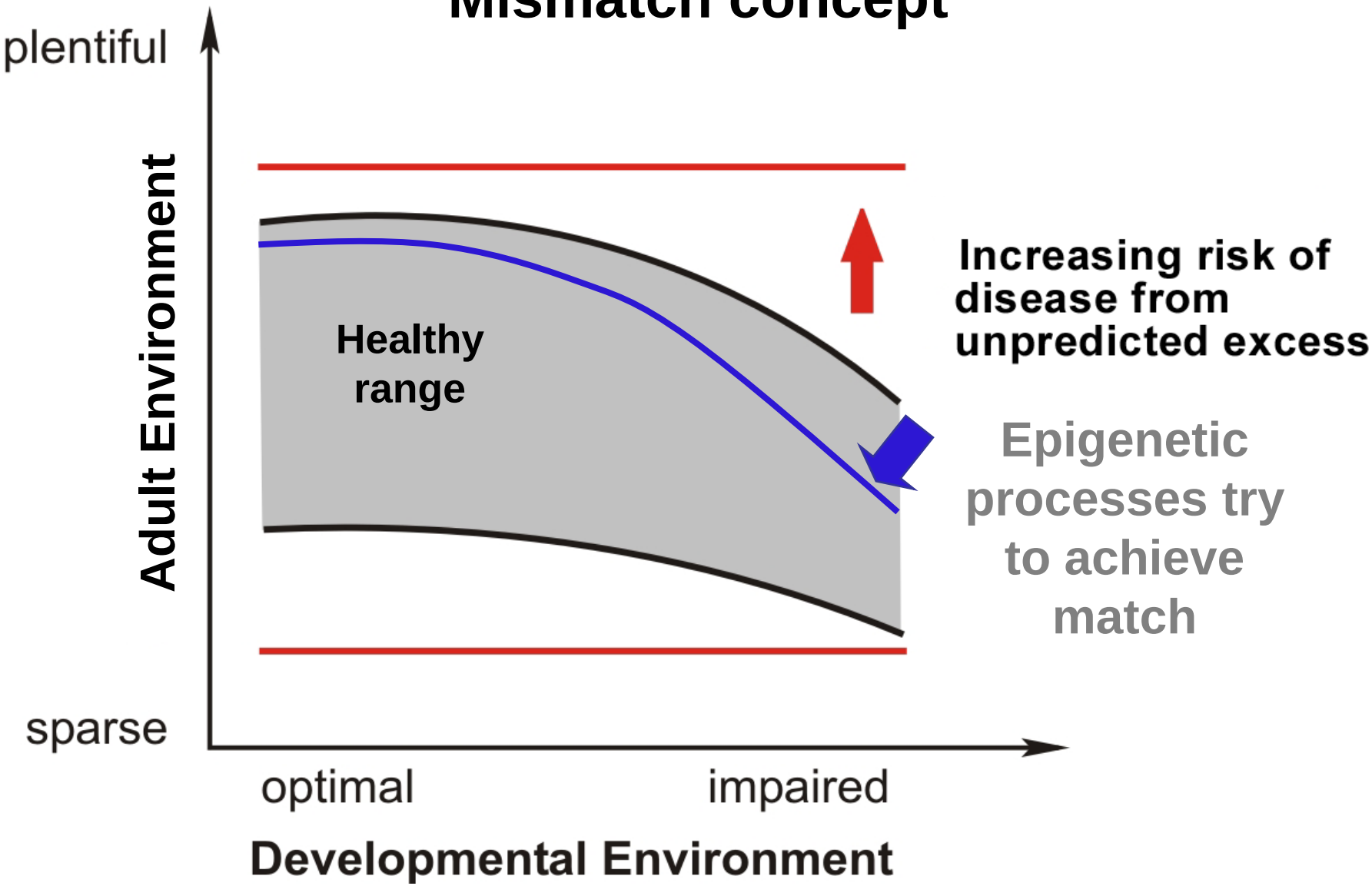
N.B. No association with mother's BMI or offspring birthweight

Godfrey et al 2011 (*Diabetes* 60: 1528- 1534)

DNA Methylation Patterns in Cord Blood DNA and Body Size in Childhood

PLoS ONE March 2012 | Volume 7 | Issue 3 | e31821

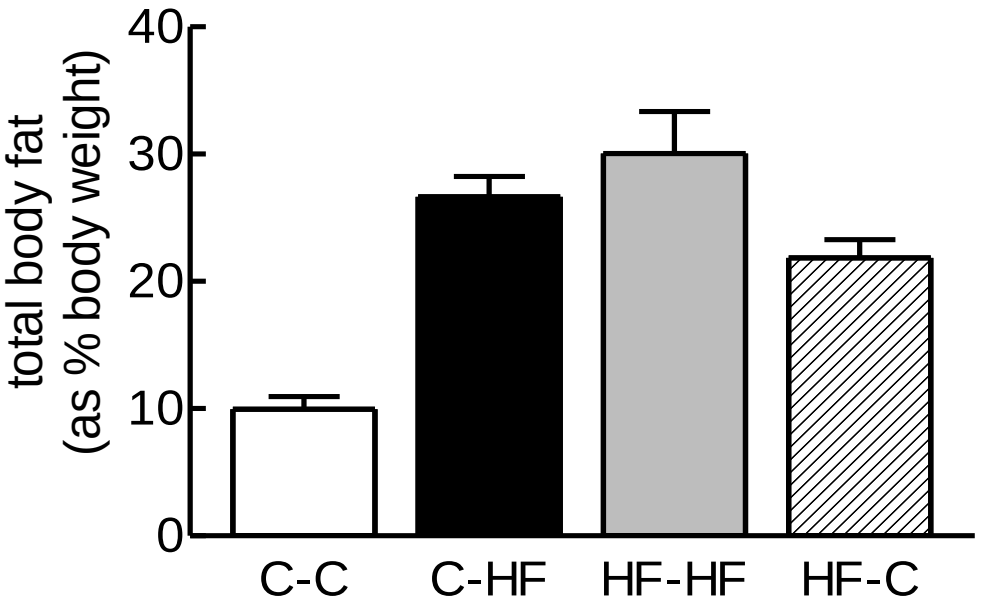
Mismatch concept

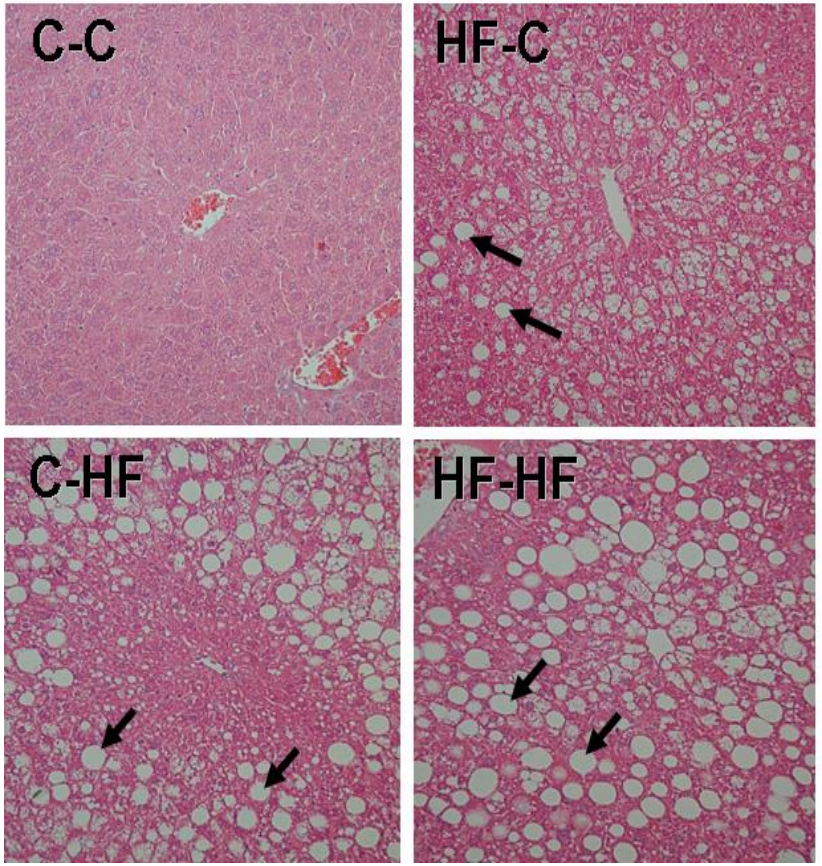


Modified from Gluckman PD, Hanson MA (2004) *Science* 305 (5691):1733-6

Chan LL, Lau WL, Leung WC

Female offspring of mice exposed to a high fat (HF) diet from weaning, through pregnancy and suckling +/- HF diet after they were weaned

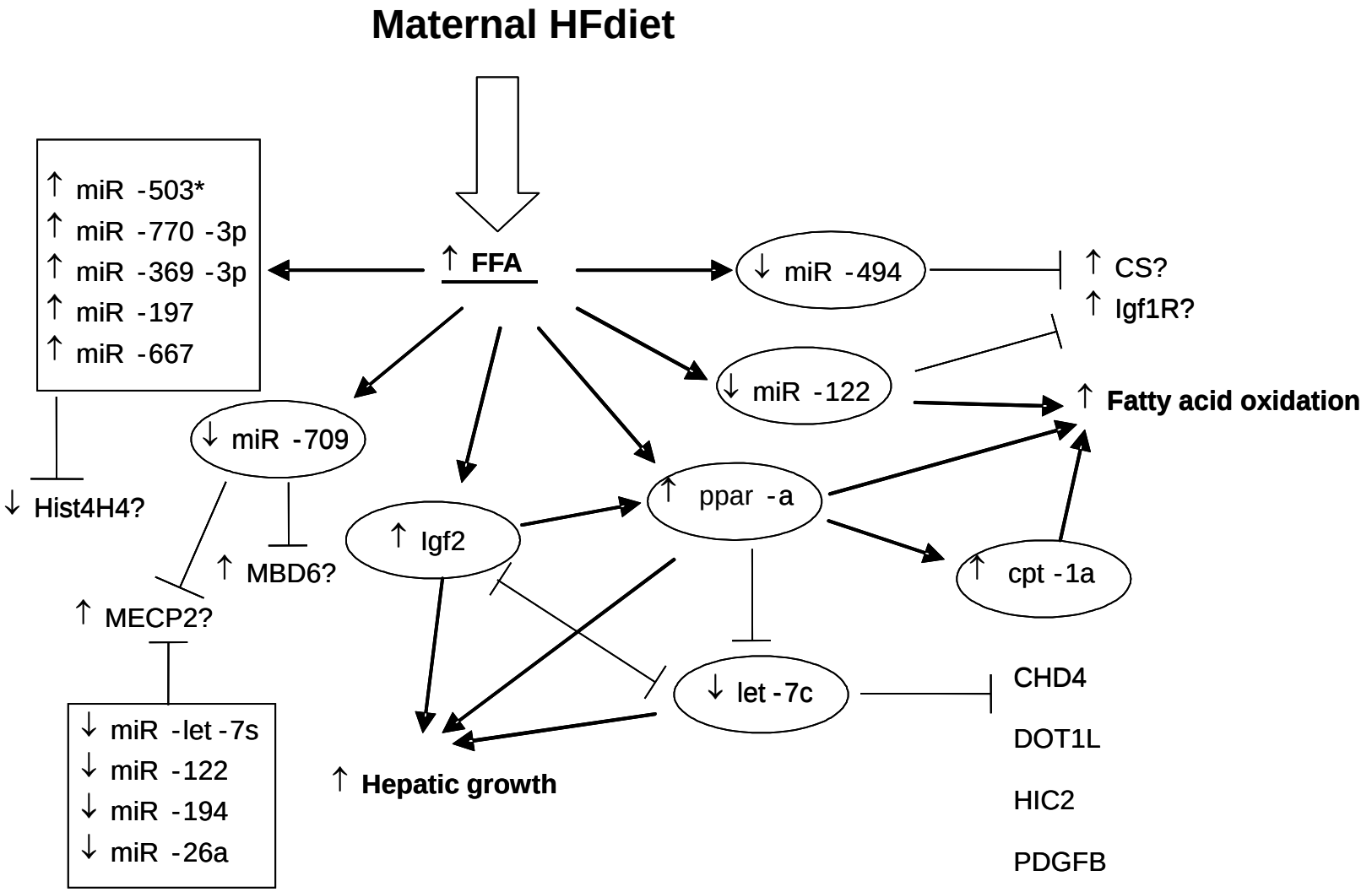




Fat deposition in liver

Elahi et al 2009

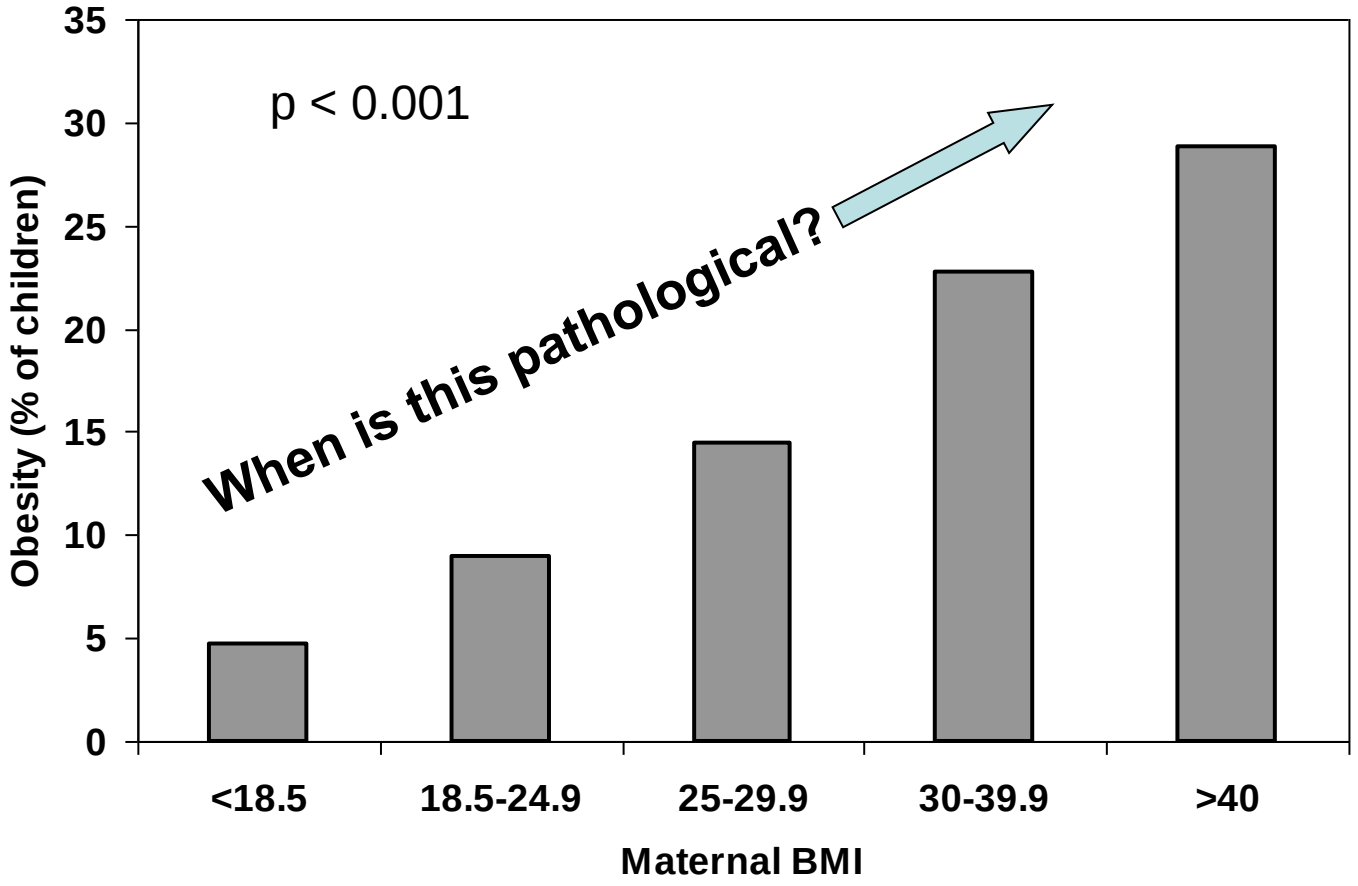
Patterns of miRNA expression



Zhang et al BMC Genomics**. 2009 16;10:478.**

What is “abnormal”?

Obesity (BMI ≥ 95th percentile) at age 4 years according to maternal first-trimester BMI



From Whitaker, Pediatrics. 2004 Jul;114(1):e29-36.

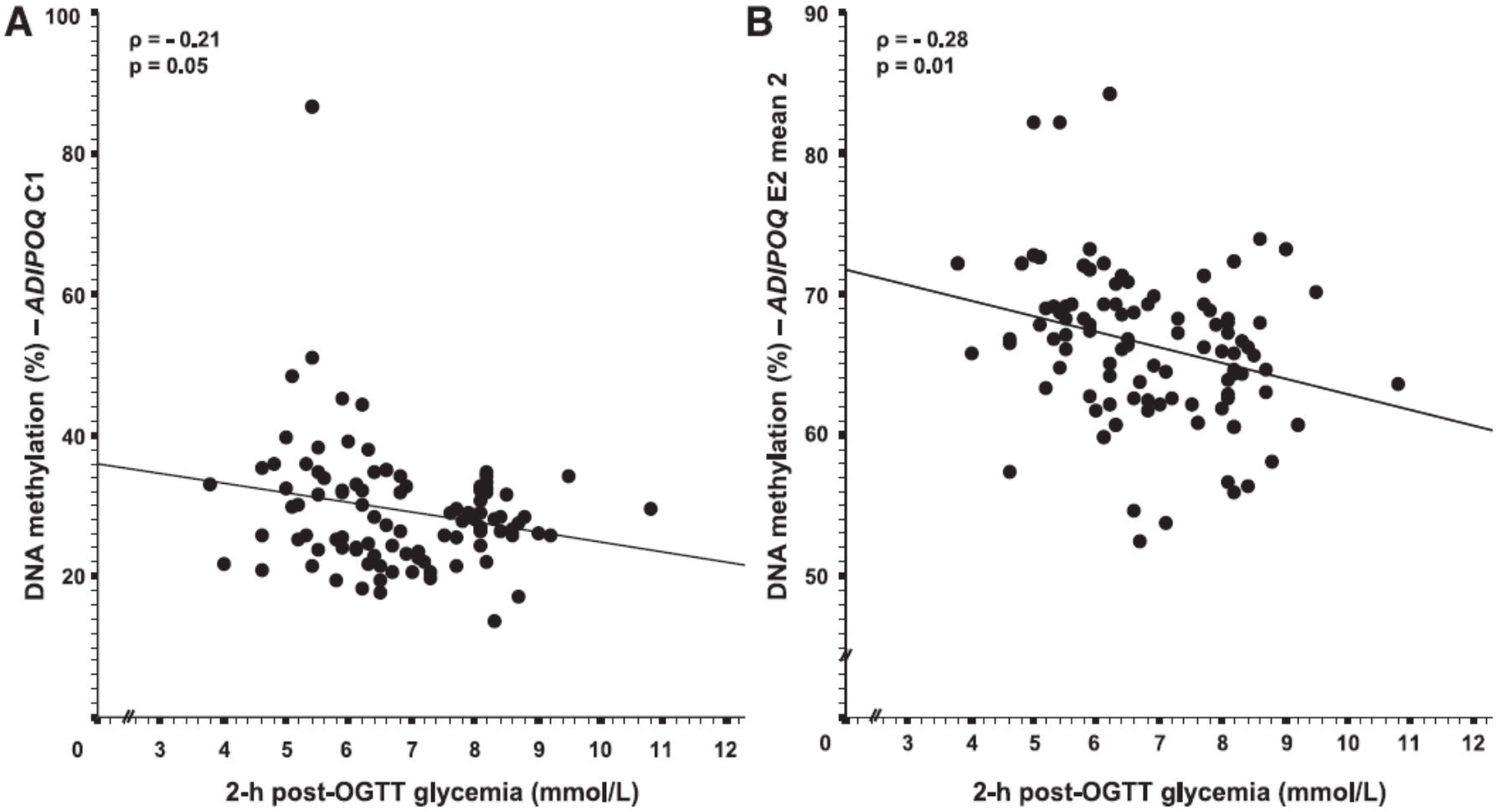


FIG. 2. Spearman correlation between placental *ADIPOQ* gene promoter DNA methylation and 2-h post-OGTT glucose levels. Adjusted for weight gain between the first and third trimester (n = 98).

Placental Adiponectin Gene DNA Methylation Levels Are Associated With Mothers' Blood Glucose Concentration

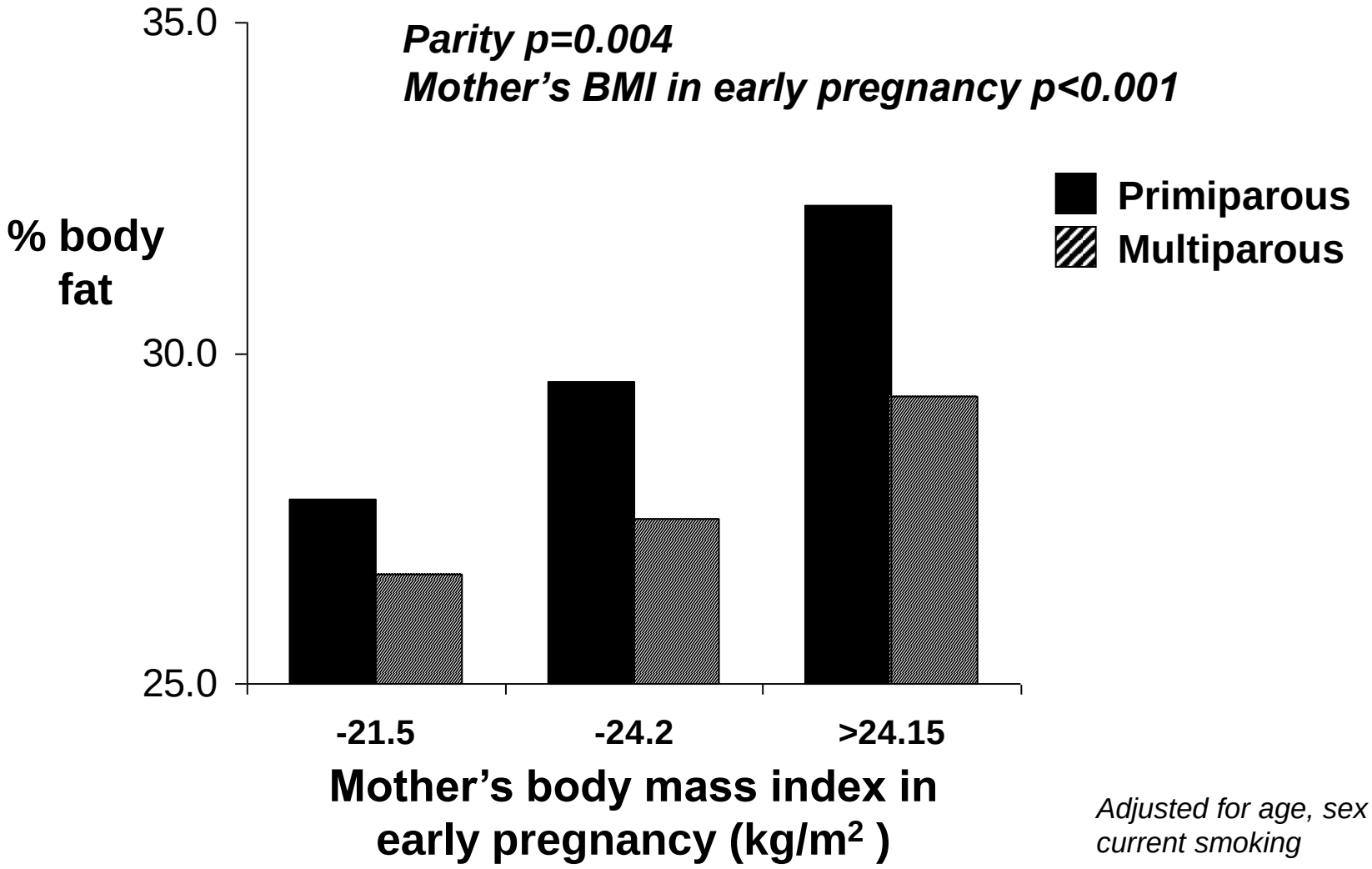
Bouchard L et al Diabetes 6 March 2012

Other demographic changes

- Falling family size
- Rising maternal age
- Higher rate of caesarean sections

Interaction between parity and mother's body composition

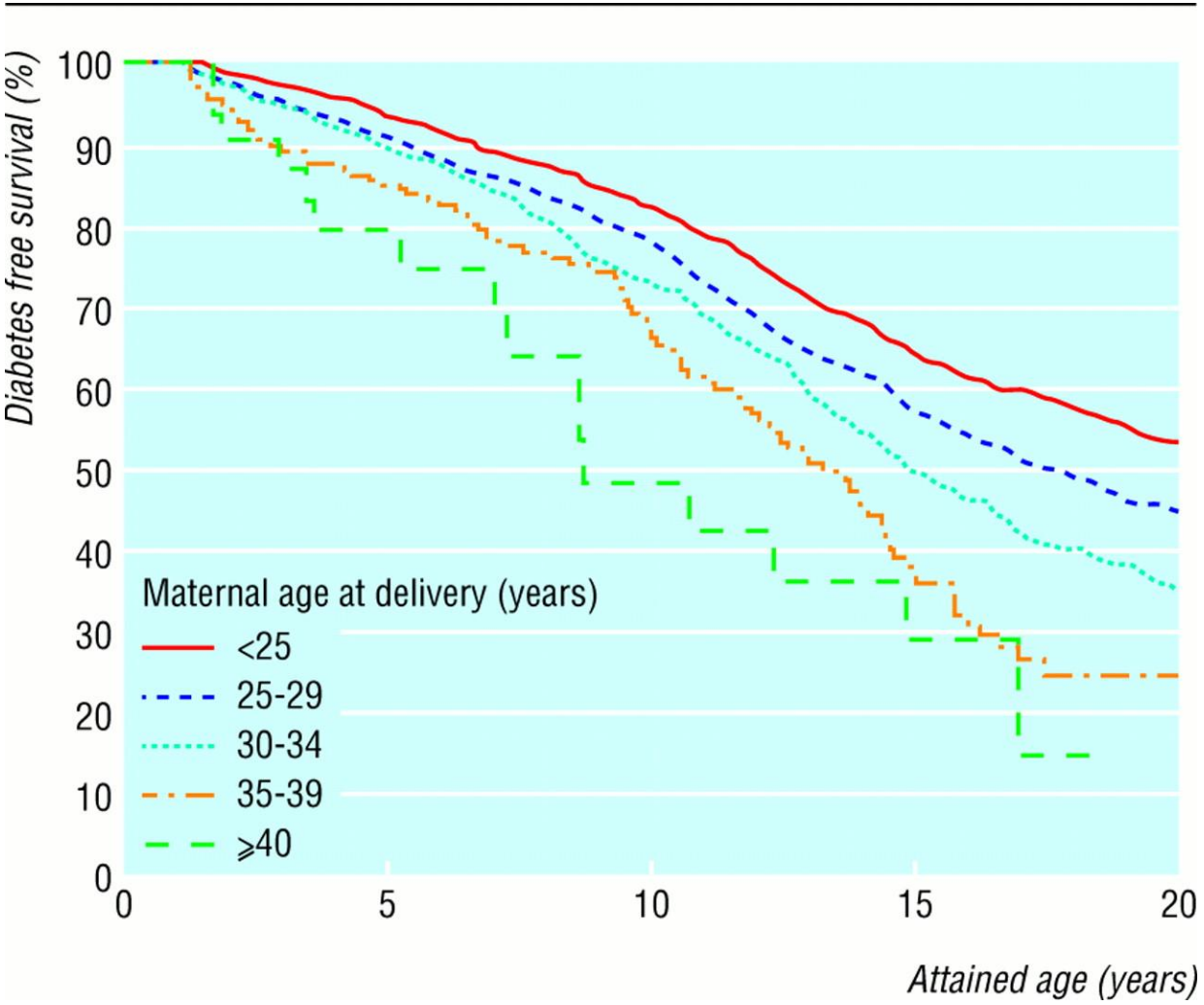
mean % body fat from skinfold thickness in 276 men & women aged 28-31 years



Adjusted for age, sex & current smoking

Reynolds & Godfrey et al (2010)

Diabetes free survival in offspring in relation to maternal age at delivery (UK).

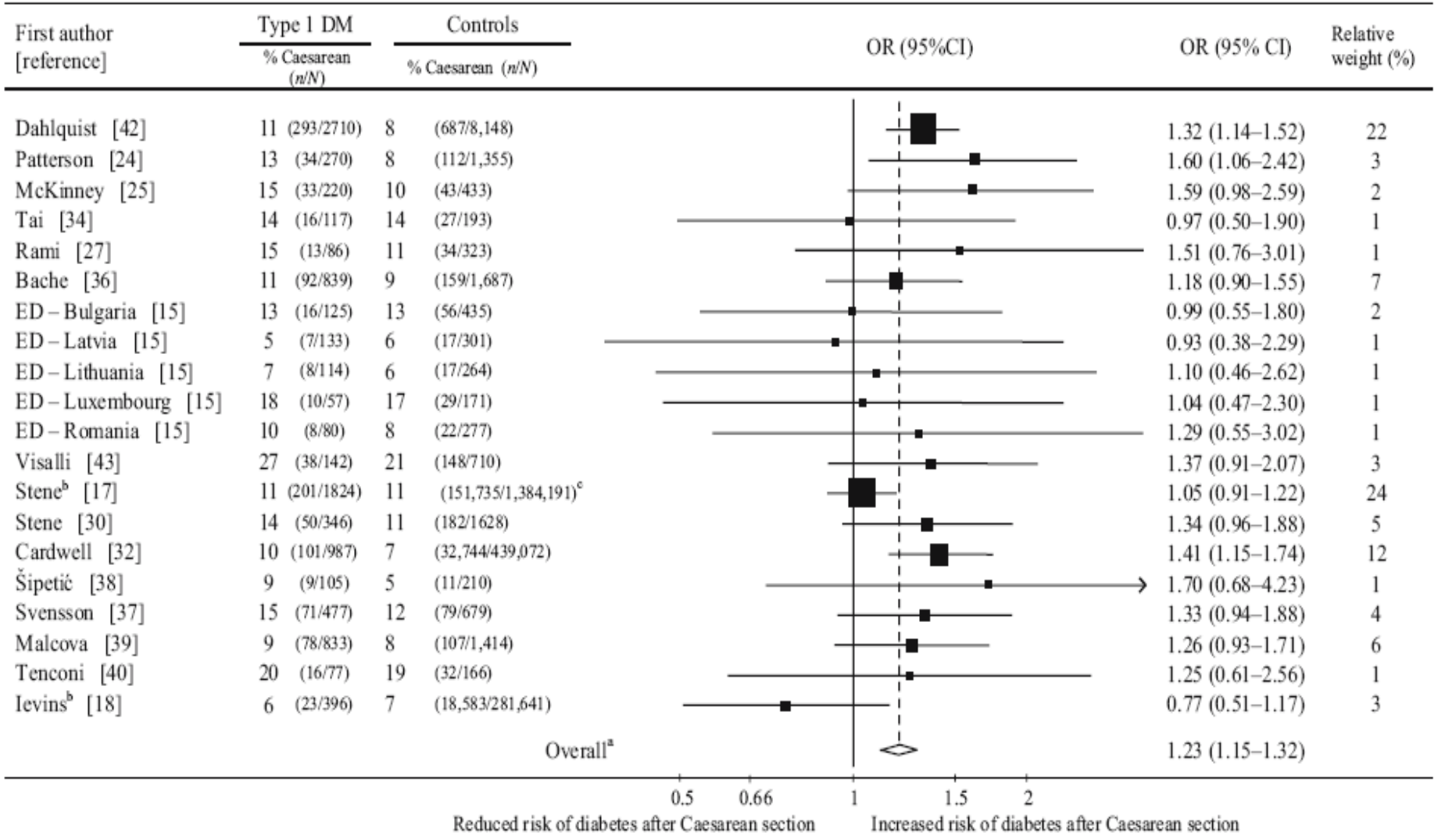


Bingley P J et al. BMJ 2000;321:420-424

Cardwell CR et al

Caesarean Section offspring

Diabetologia (2008) 51:726–735



Interventions

- Success may depend on epigenetic status in individual

Differential epigenomic and transcriptomic responses in subcutaneous adipose tissue between low and high responders to caloric restriction.

Bouchard L et al (2010) *Am J ClinNutr*; **91**:309–20.

- Significant DNA methylation differences at 35 loci were found between the high and low responders before dieting, with 3 regions showing differential methylation after intervention.
- Some of these regions contained genes known to be involved in weight control and insulin secretion, whereas others were localized in known imprinted genomic regions.
- Differences in gene expression profiles were observed only after dieting, with 644 genes being differentially expressed between the 2 groups.
- These included genes likely to be involved in metabolic pathways related to angiogenesis and cerebellar long-term depression.

Interventions

- Animal models provide proof of principle for efficacy of pharmacological (e.g. statin), endocrine (leptin) and nutritional (folate, methyl donors) interventions

Interventions

- Animal models provide proof of principle for efficacy of pharmacological (e.g. statin), endocrine (leptin) and nutritional (folate, methyl donors) interventions
- Encouraging evidence is emerging in human, but effective interventions will involve wider social support

Tobias DK et al (2012) Pre-pregnancy adherence to dietary patterns and lower risk of gestational diabetes mellitus Am J Clin Nut: 96 289-95

Quartiles of prepregnancy dietary pattern adherence scores and GDM risk[1]

	Q1[2]	Q2	Q3	Q4	*P*-trend
aMED					
GDM/pregnancies	221/4601	321/7366	147/4134	183/5275	
Model 1	1.0	0.87 (0.73, 1.03)[3]	0.66 (0.53, 0.82)	0.61 (0.49, 0.75)	<0.0001
Model 2	1.0	0.89 (0.74, 1.06)	0.70 (0.57, 0.88)	0.67 (0.54, 0.84)	0.0001
Model 3	1.0	0.95 (0.79, 1.14)	0.76 (0.60, 0.95)	0.76 (0.60, 0.95)	0.004
DASH					
GDM/pregnancies	232/4213	220/5573	227/5806	193/5784	
Model 1	1.0	0.69 (0.57, 0.83)	0.66 (0.54, 0.79)	0.52 (0.42, 0.64)	<0.0001
Model 2	1.0	0.75 (0.61, 0.90)	0.74 (0.61, 0.90)	0.61 (0.49, 0.76)	<0.0001
Model 3	1.0	0.77 (0.63, 0.93)	0.78 (0.64, 0.95)	0.66 (0.53, 0.82)	0.0005
aHEI					
GDM/pregnancies	242/4661	252/5261	203/5313	175/6141	
Model 1	1.0	0.86 (0.72, 1.04)	0.64 (0.53, 0.79)	0.44 (0.36, 0.54)	<0.0001
Model 2	1.0	0.90 (0.74, 1.08)	0.67 (0.55, 0.81)	0.46 (0.37, 0.57)	<0.0001
Model 3	1.0	0.96 (0.79, 1.15)	0.75 (0.61, 0.91)	0.54 (0.43, 0.68)	<0.0001

UNIVERSITY OF Southampton
School of Medicine

Paternally Induced Transgenerational Environmental Reprogramming of Metabolic Gene Expression in Mammals

Carone BR et al (2010) *Cell* **143**, 1084–1096.

Offspring of *males* fed a low-protein diet exhibited elevated hepatic expression of many genes involved in lipid and cholesterol biosynthesis and decreased levels of cholesterol esters, relative to the offspring of males fed a control diet. Epigenomic profiling of offspring livers revealed numerous modest (20%) changes in cytosine methylation depending on paternal diet, including reproducible changes in methylation over a likely enhancer for the key lipid regulator PPARa.

New Insights - Summary

- We need a new medical model for NCDs
- There is a very strong case for interventions in early life for NCD prevention
- We have biomarkers of later NCD risk which can be measured in early life
- We have moved from focusing on low birthweight to realise that effects on NCD risk are graded across the entire normal range of development
- NCDs do not *start* in development, but development influences responses to later challenges and so risk
- Pre-conception period may be critical in terms of health literacy and behaviour or parents-to-be
- Needs a focus on adolescent girls (and boys too)
- Promoting a healthy start to life means that we could show a beneficial effect of interventions within a short (<5 years) timeframe.

United Nations (Sept 2011)**:**
Political declaration of the High-level Meeting of the General Assembly on the Prevention & Control of Non-communicable Diseases

14. In 2008, an estimate 36 million of the 57 million global deaths were due to NCDs, ... and that nearly 80% of those deaths occurred in developing countries

26. {We} note also with concern that maternal and child health is inextricably linked with NCDs and their risk factors, specifically as prenatal malnutrition and low birth weight create a predisposition to obesity, high blood pressure, heart disease and diabetes later in life; and that pregnancy conditions, such as maternal obesity and gestational diabetes, are associated with similar risks in both the mother and her offspring

37. Acknowledge the contribution and important role played by all relevant stakeholders, including individuals, families, and communities, intergovernmental organizations and religious institutions, civil society, academia, media, voluntary associations, and where and as appropriate, the private sector and industry, in support of national efforts for NCD prevention and control

Welcome to DOHaD 2013