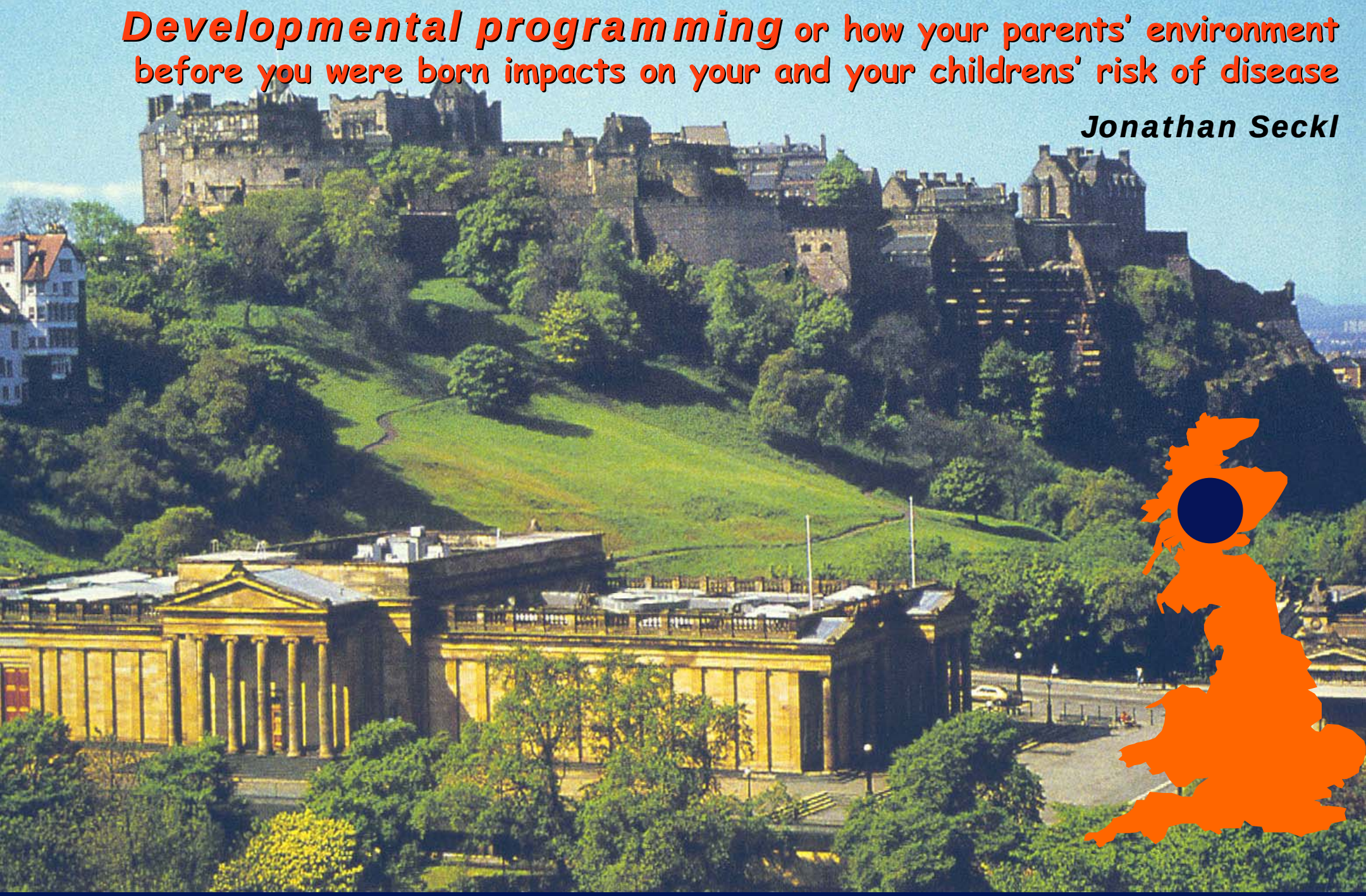
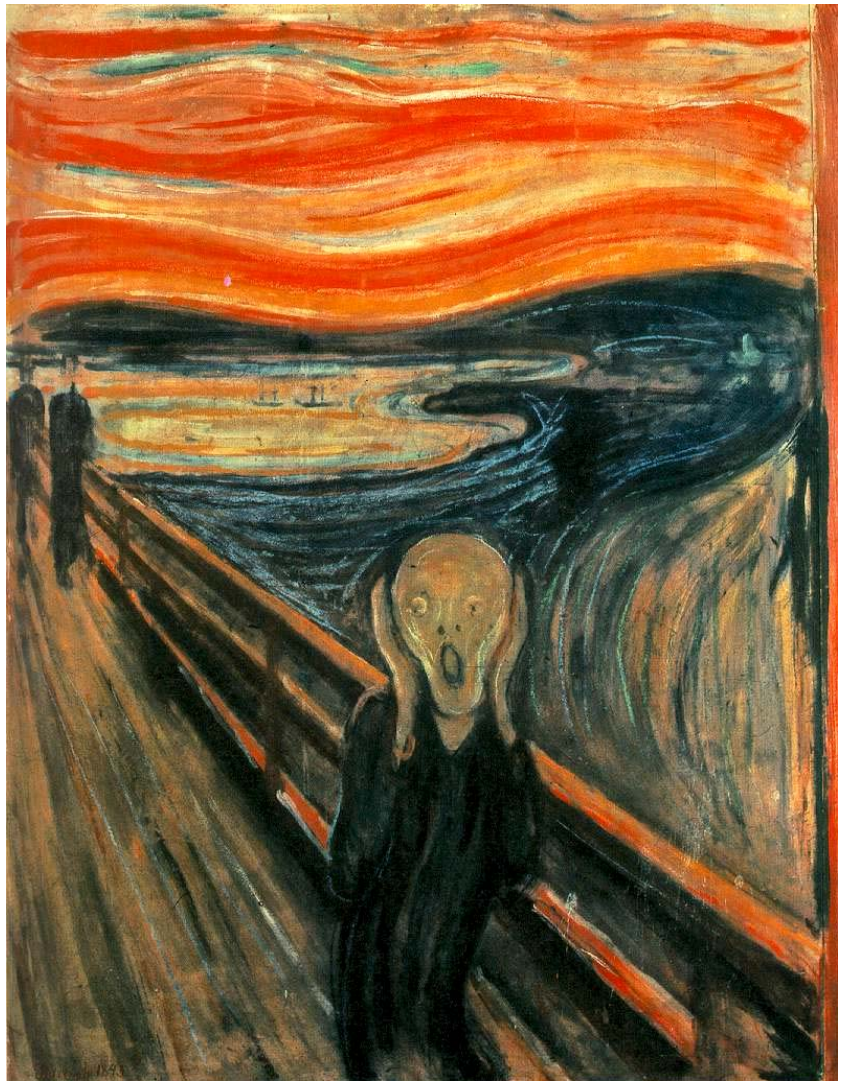
Developmental programming or how your parents' environment before you were born impacts on your and your childrens' risk of disease

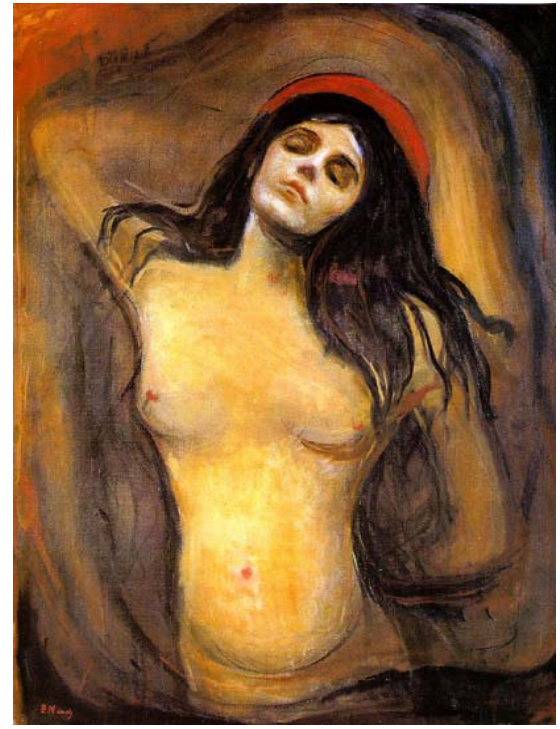
Jonathan Seckl



Scottish Cuisine and disease

Stress

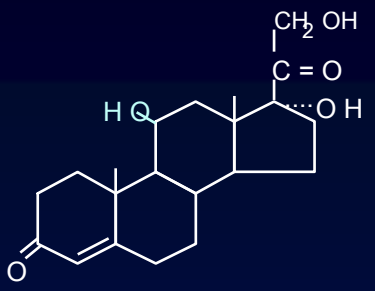




"Without stress, there would be no life"

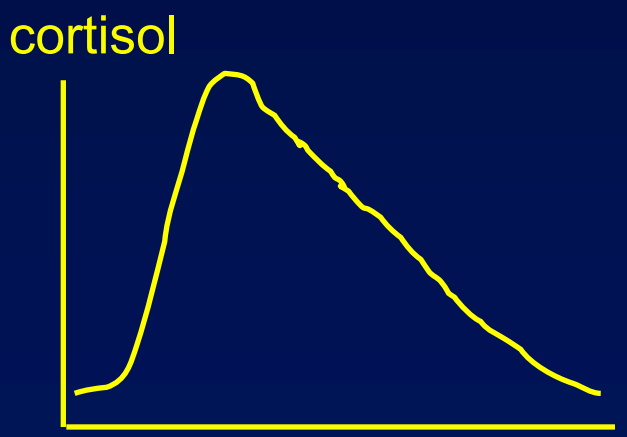
Hans Selye

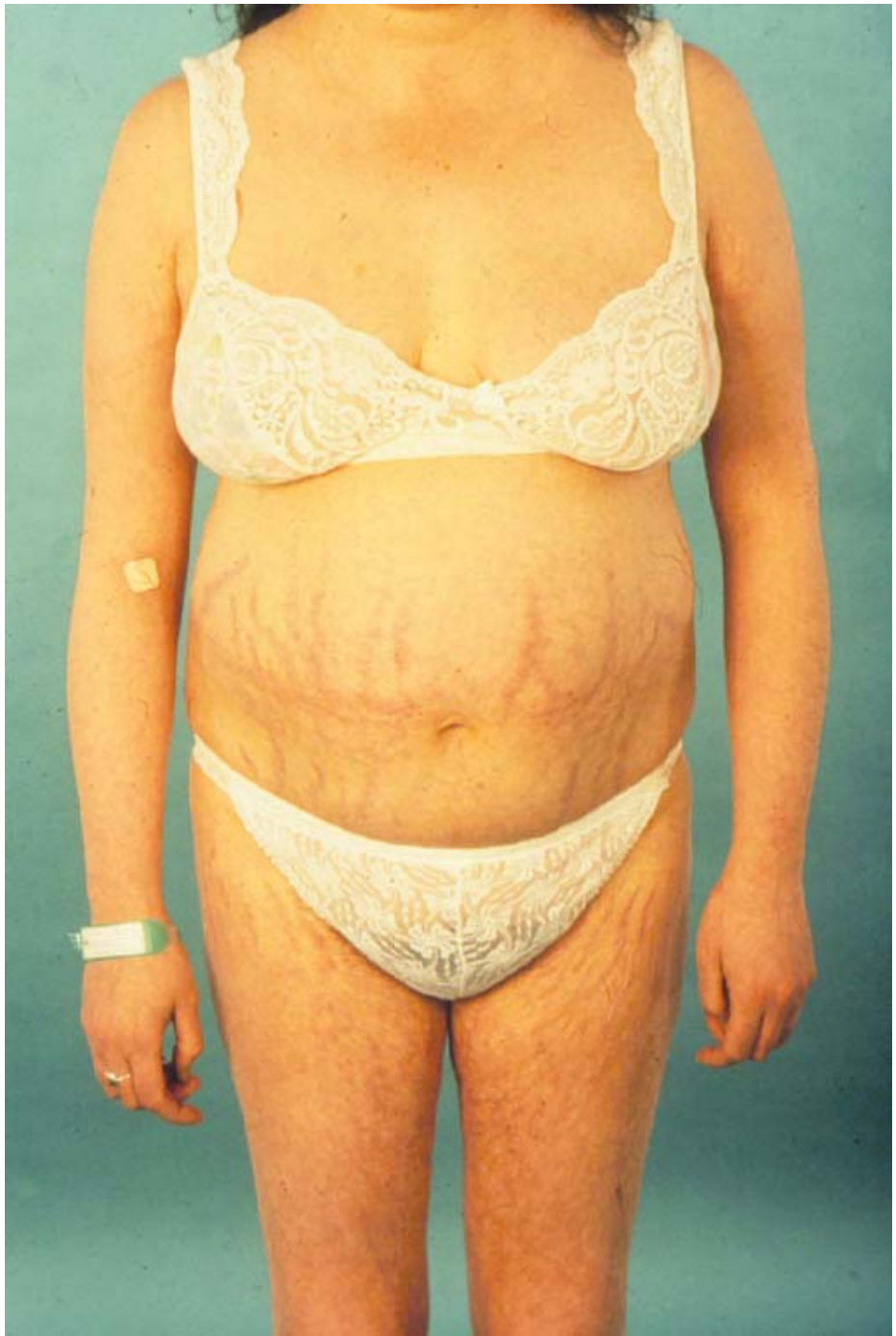
Glucocorticoids

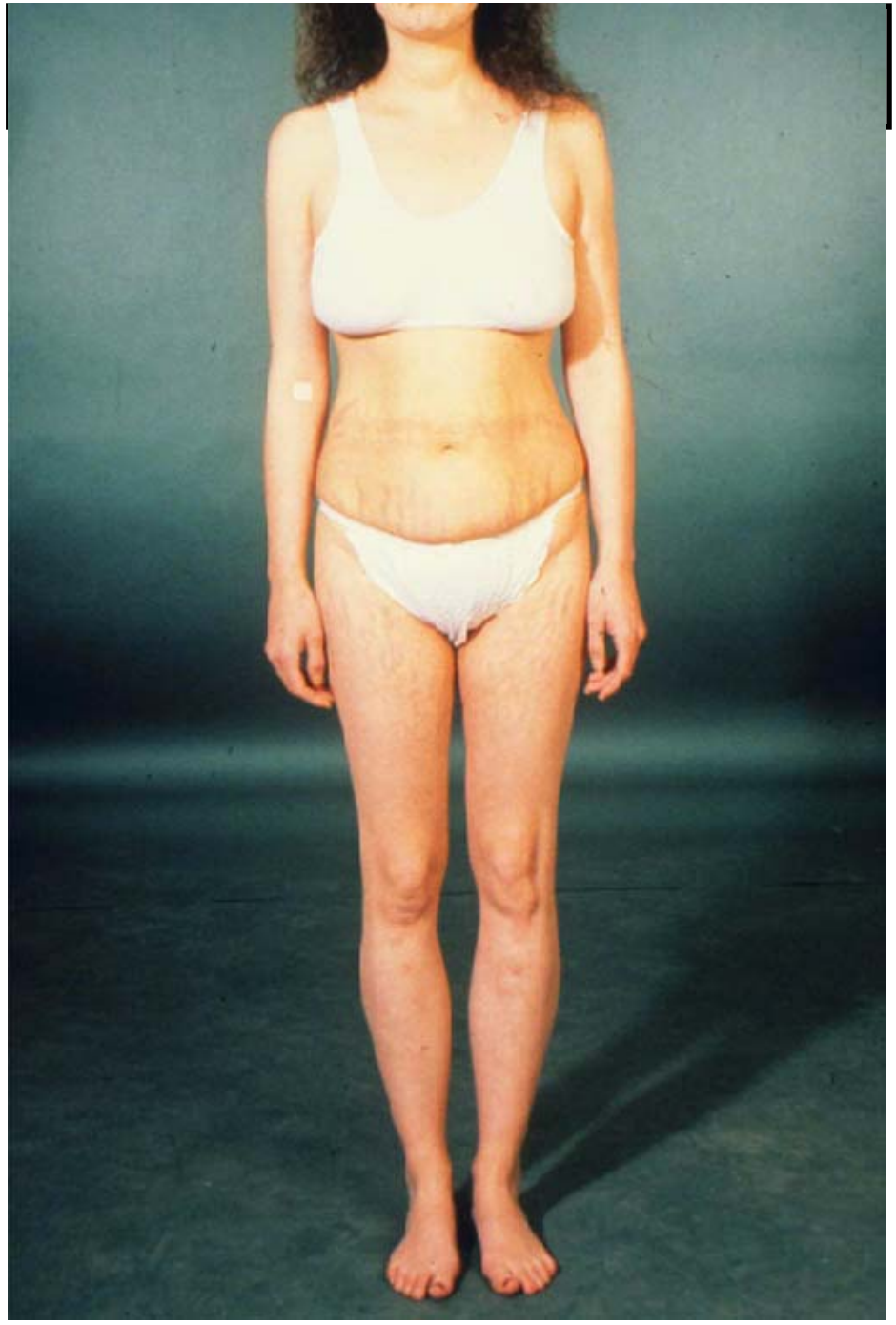


Cortisol

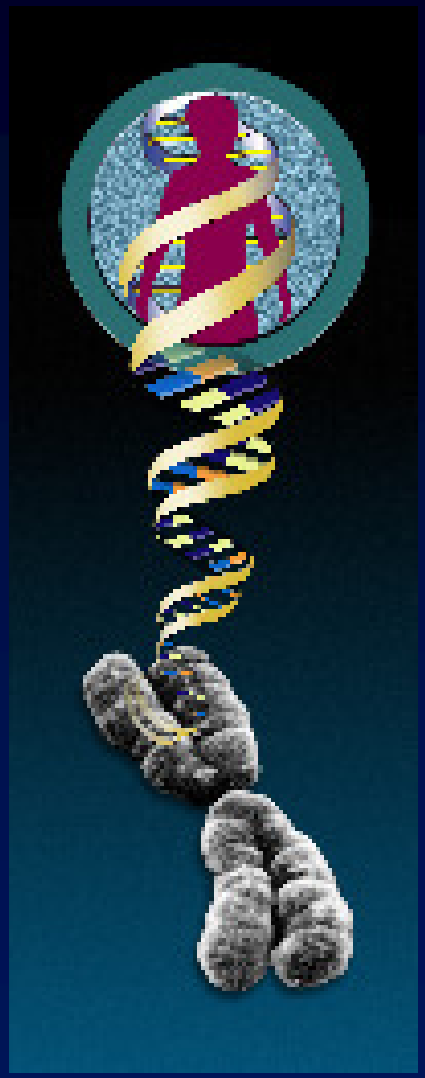
- Mobilise fuel
  - Glucose
  - Fatty acids
  - Proteins
- Increase blood pressure
- Euphoria
- Inhibit
  - inflammation
  - immune responses
  - wound healing
  - digestion
  - growth/bone formation
  - reproduction
  - detailed learning and memory







Nature and nurture



X


Virginia
Virginia


SCHWARZENEGGER DEVITO
TWINS
DVD

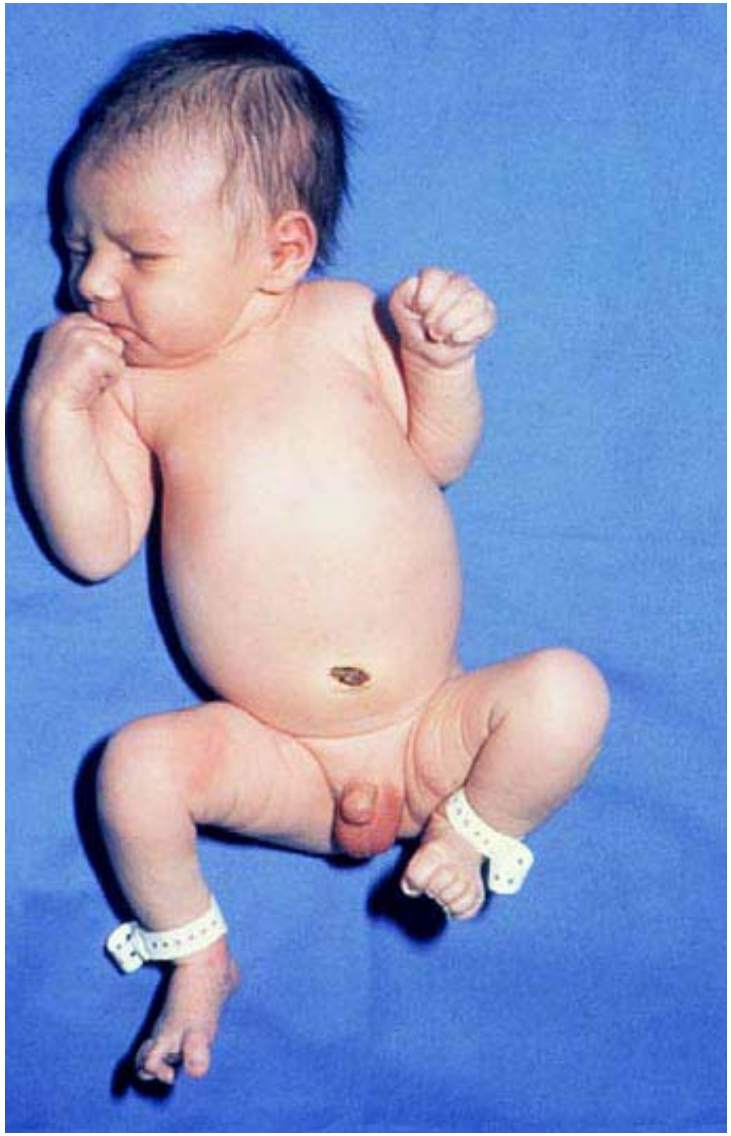
But

Identical twins reared *apart* from birth (same genes, different environment)……

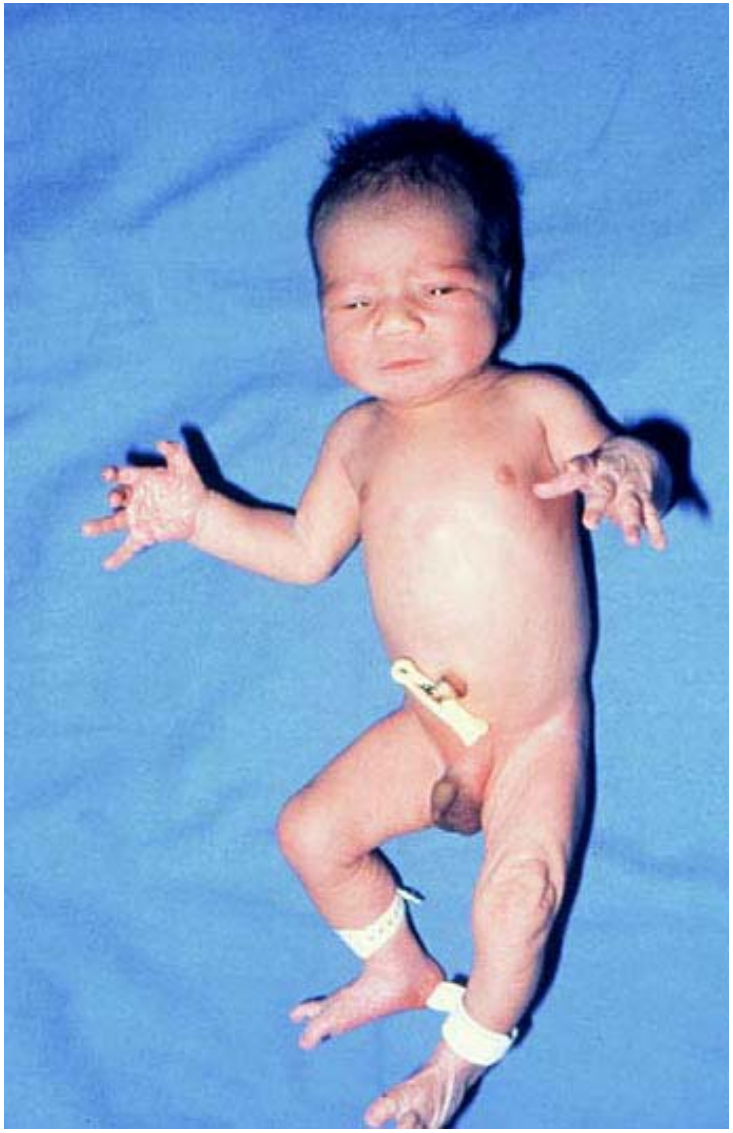
have the *same concordance* of many diseases (schizophrenia, diabetes, etc) as those reared together (same genes, same environment).

This suggests that the environmental factors that underlie the *differences between identical twins* operate BEFORE or at birth.

Birth weight and adult disease



8.5 lbs (~4 kg)



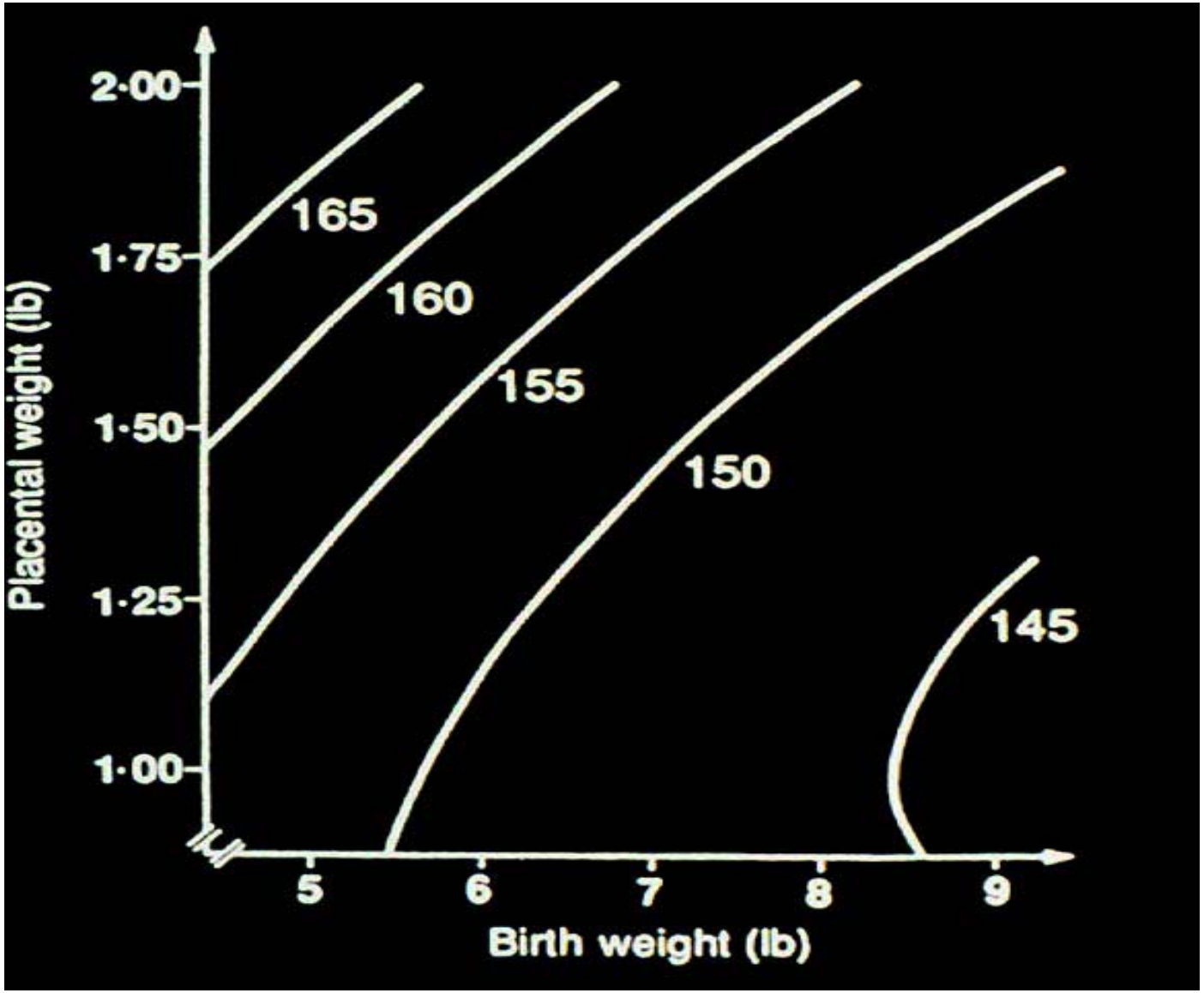
5.5 lbs (~2.4 kg)

Ethel Margaret Burnside

Hertfordshire's 'Lady Inspector of Midwives' (1911-30)

Weight at Birth.	Weight 1st Year	Food.	No. of Visits.	Condition, and Remarks of Health Visitor. W	V.	D	T
8¼ lbs	24½ lbs	B.	11	4	-	-	4
Healthy & well developed.				Buckland School.		Card to S.	
7 lbs	15¼ lbs	B	12	h.	4.	4.	8
Moved to Bury Green Lt.			Hadham.	Had measles pneumonia &			
8	20	B.C.	11	Y.	Y.	?	4
T.B. above in of neck opened. Ant. fontanelle still open @ 3 yrs. Abdomen very large & pr							
8½	22	B.B.	9	Y	Y	Y	10
Healthy & normal.				Buckland	School.	Card.	

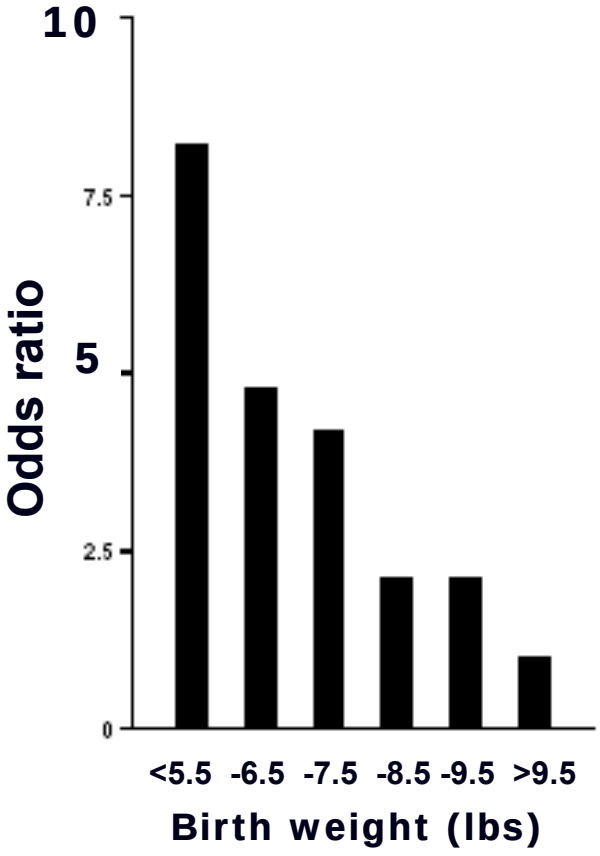
Birth weight and adult disease



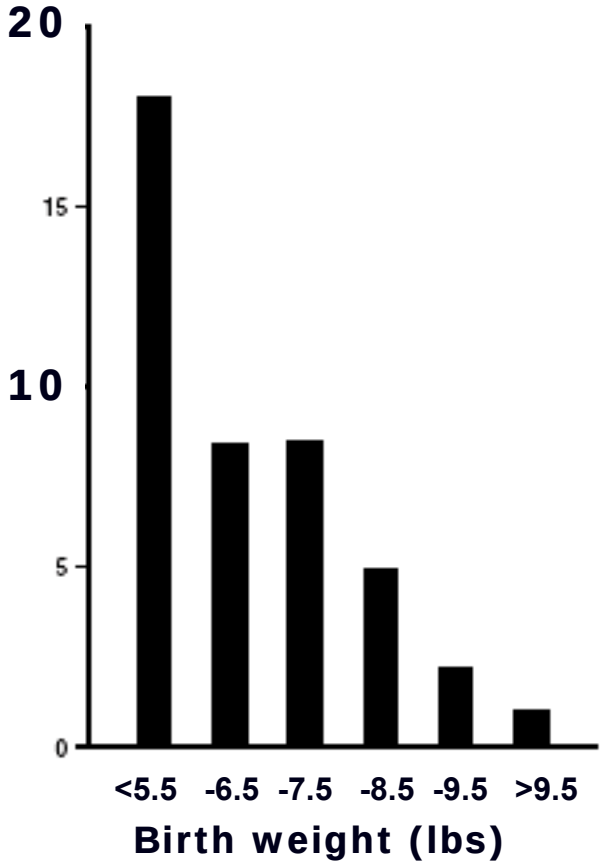
Barker et al, 1990, BMJ, 301:259

Low birth weight and risk of T2D/MS

Type 2 diabetes



Metabolic syndrome



JAMA®

Online article and related content current as of January 19, 2009.

Birth Weight and Risk of Type 2 Diabetes: A Systematic Review

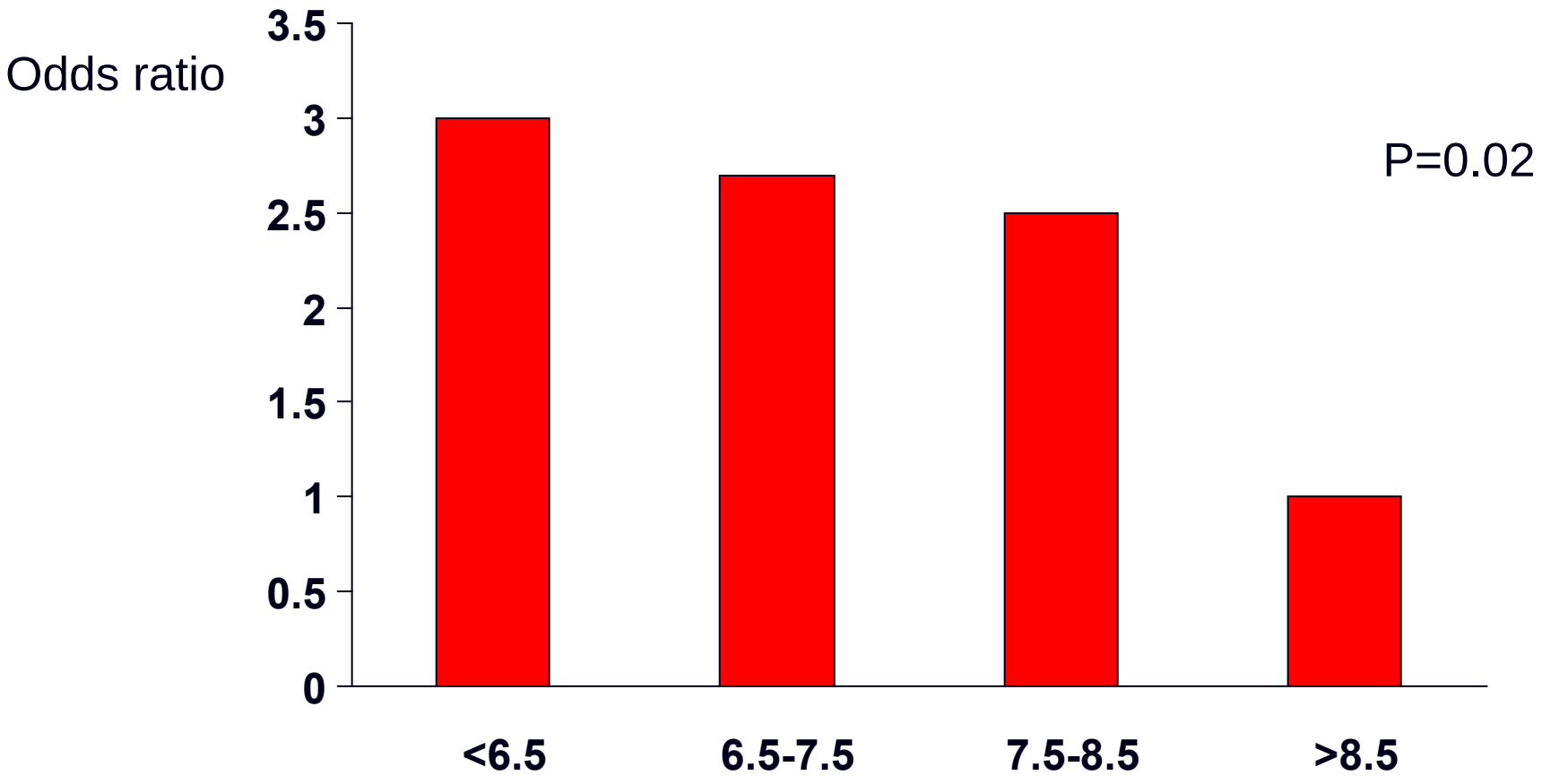
Peter H. Whincup; Samantha J. Kaye; Christopher G. Owen; et al.

JAMA. 2008;300(24):2886-2897 (doi:10.1001/jama.2008.886)

- 30 reports, 152000 subjects
- Pooled OR 0.75/kg
  (CI 0.70-0.81)
- Not reduced by adjusting:
  - adult BMI
  - SE status

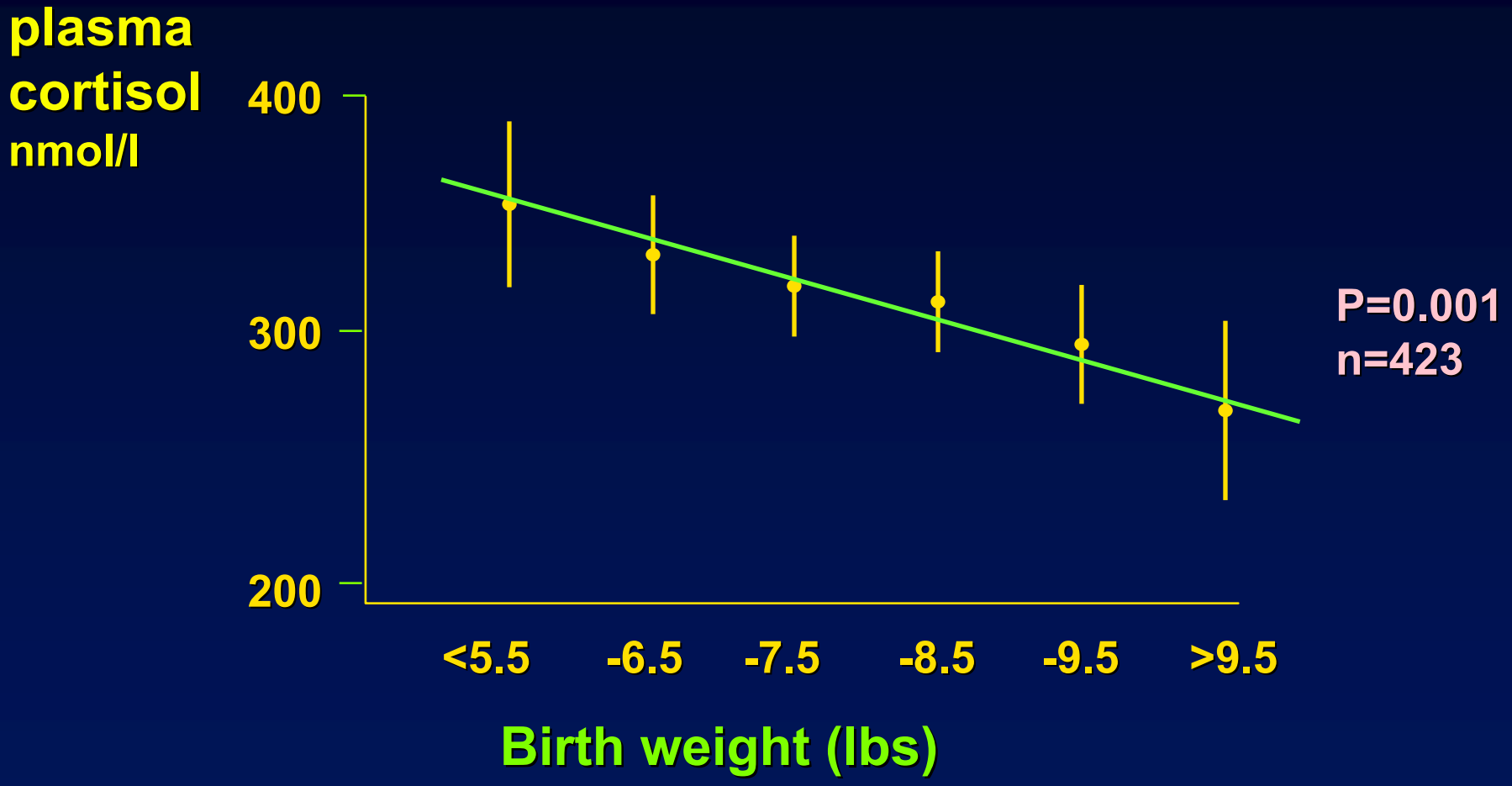
Hales et al, BMJ 1991; *Barker et al, Diabetologia 1993;* *Whincup et al, JAMA 2008*

Birth weight and depression aged 68 years



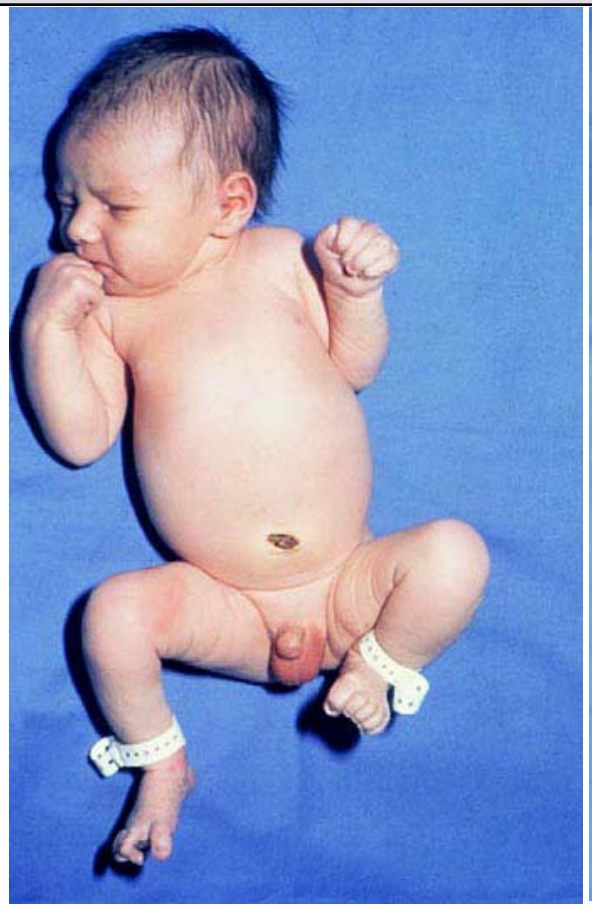
from the Hertfordshire cohort study: Thompson et al BJPsych 2001

Plasma cortisol in 64y old men correlates negatively with birth weight

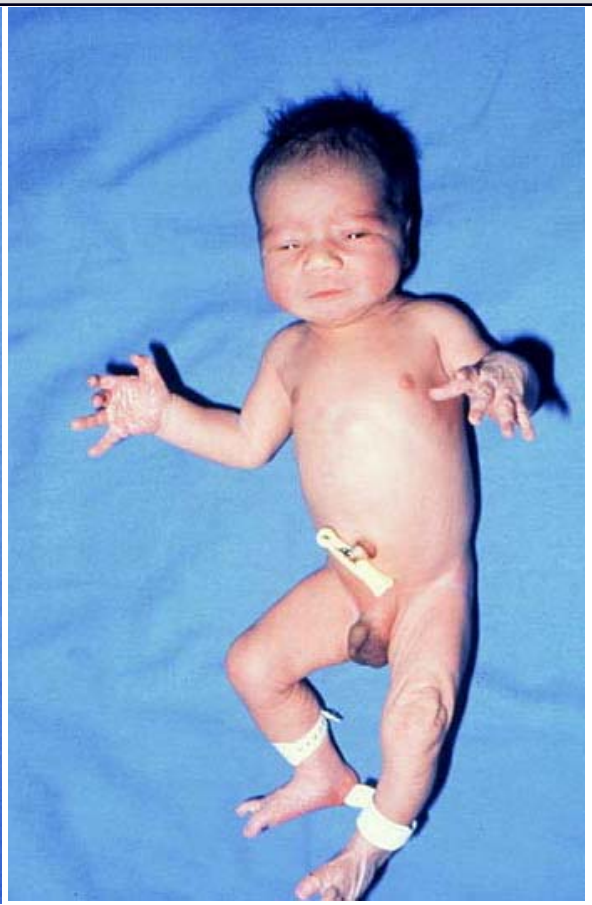


Phillips et al, *JCE&M*, 1998

Birth weight and adult disease



8.7 lbs
4 kg



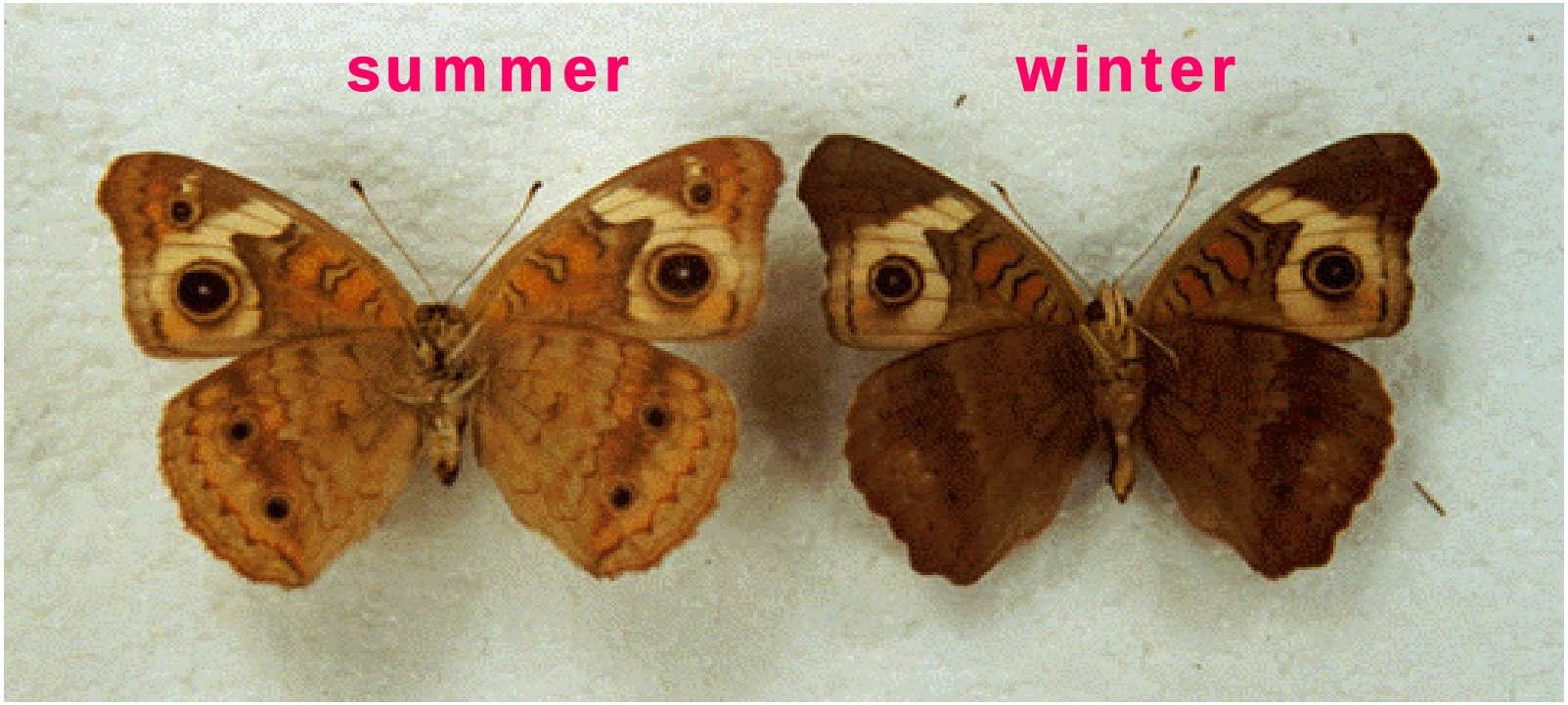
5.3 lbs
2.4 kg

low birth weight

- hypertension
- type 2 diabetes
- hyperlipidaemia
- metabolic syndome
- coronary heart disease
- osteoporosis
- depression, anxiety, psychosis

- *Increased overall mortality*

The environment and regulation of development



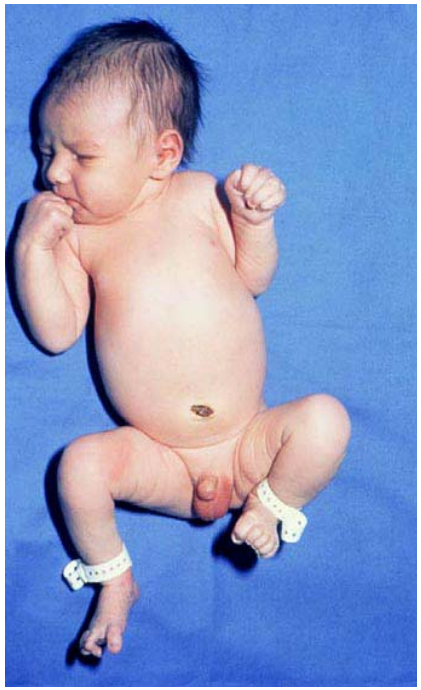
- Butterflies hatched during different seasons were coloured differently
- Season-dependent colouration mimicked by larval incubation temperature

Weissman 1893

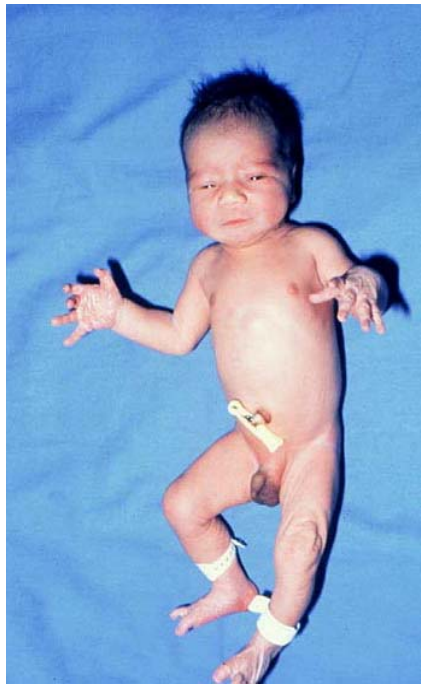
Developmental programming is not about disease

- The phenomenon is widespread (ubiquitous)
- It is adaptive
  - In a famine-striken warzone the 'small baby' phenotype appears beneficial (low birth weight, rapid growth, higher BP, waryness, early puberty, etc)
- A tiny improvement in individual survival over *evolutionary time* would maintain the processes
- Associations with disease reflect contemporary concerns and miss the underlying biology
- We do not (yet) understand most of the 'rules'
  - low b. wt is a blunt marker of '*something challenging happened*'

Mechanisms linking to adult disease



8.7 lbs (4 kg)

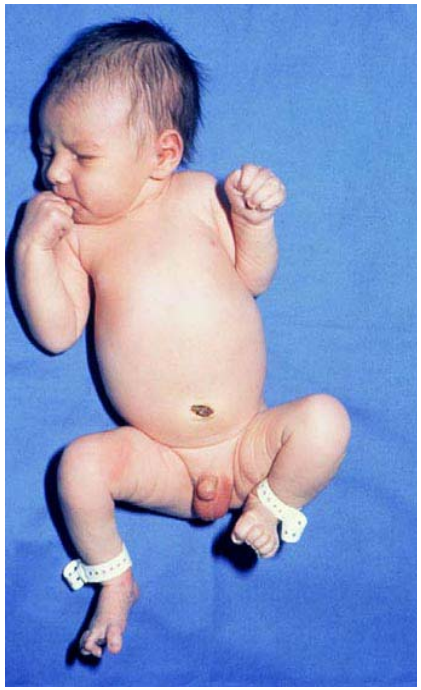


5.3 lbs (2.4 kg)

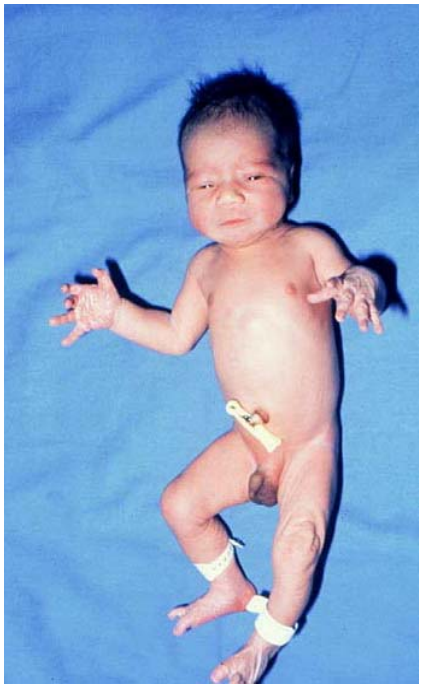
Possible mechanisms

- genetics

Mechanisms linking to adult disease



8.7 lbs (4 kg)

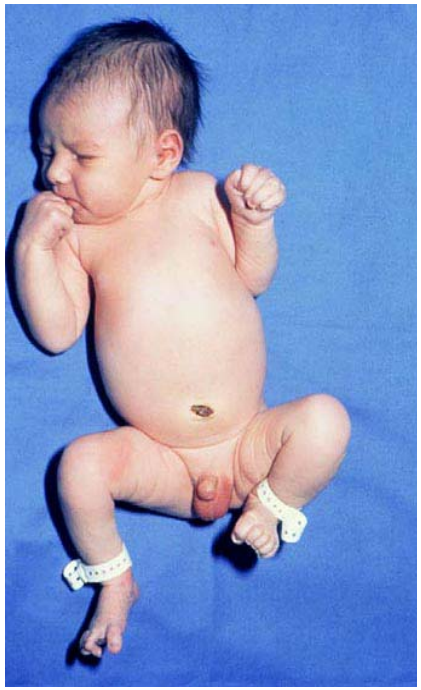


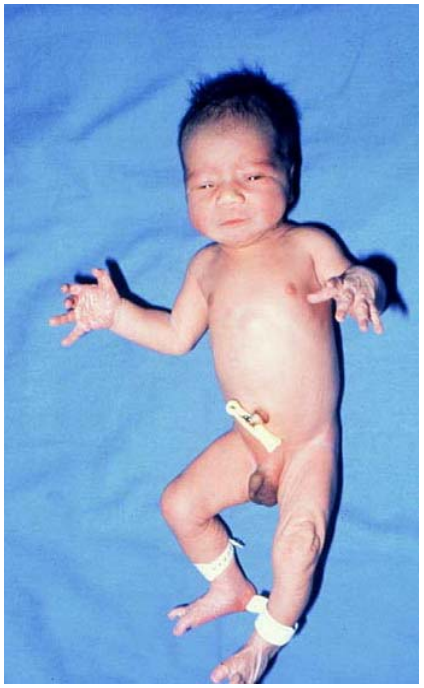
5.3 lbs (2.4 kg)

Possible mechanisms

- genetics
- Socio-economic class

Mechanisms linking to adult disease





8.7 lbs (4 kg) **5.3 lbs (2.4 kg)**

Possible mechanisms

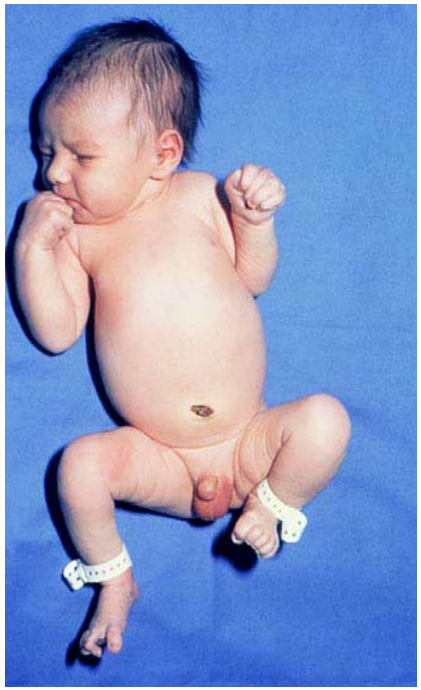
- genetics
- socio-economic class
- maternal malnutrition

Pre-natal starvation…
Dutch Hunger Winter 1945 and Chinese Famine 1959-61

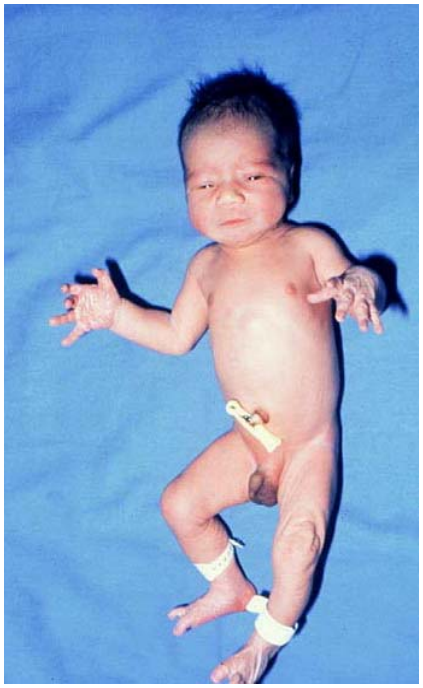
'We Were So Hungry We Ate Tulips'
Father Leo Zonneveld

offspring show:-
- small reduction in birth weight
- increased schizophrenia
- addiction and depression
- increased diabetes
- increased blood pressure
- more heart disease
- higher cortisol levels

Mechanisms linking to adult disease



8.7 lbs (4 kg)



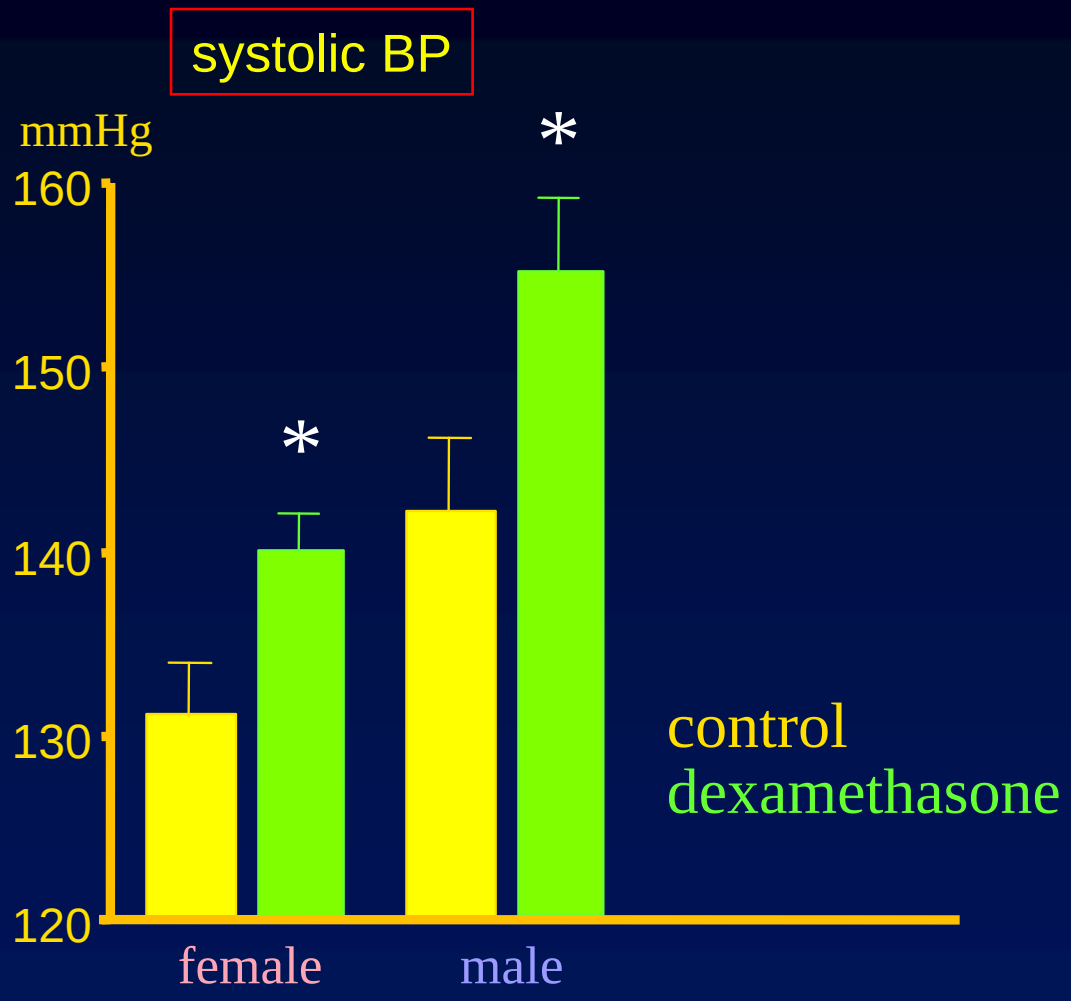
5.3 lbs (2.4 kg)

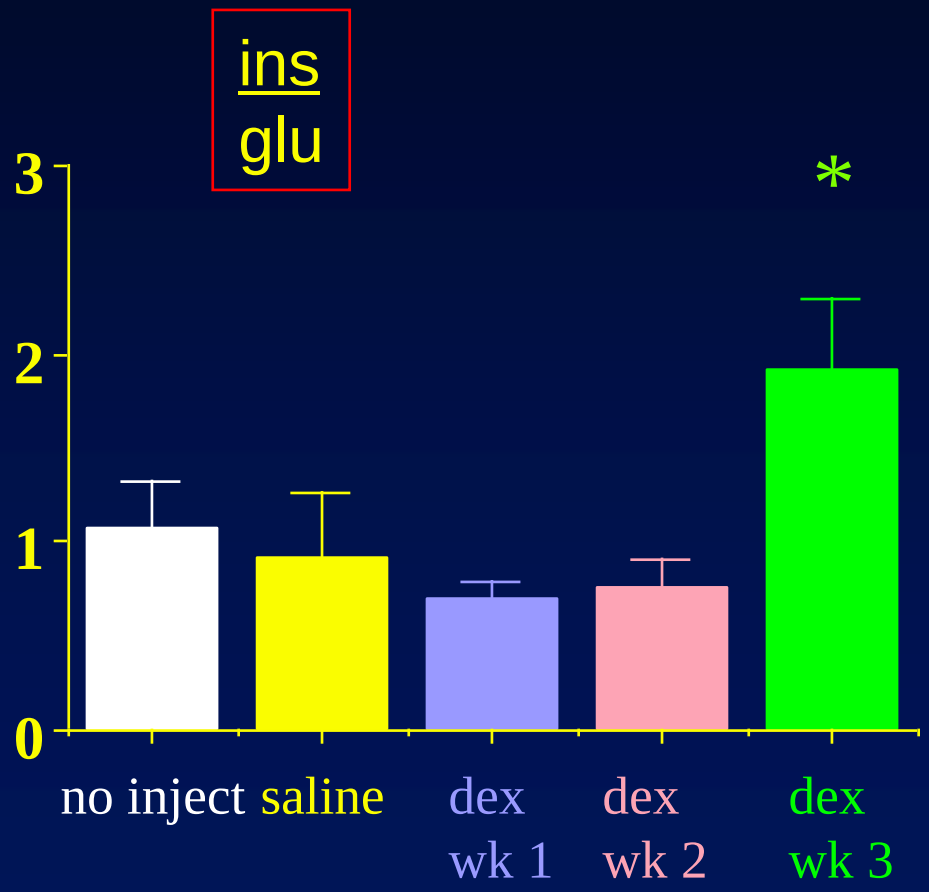
Possible mechanisms

- genetics
- social class
- maternal malnutrition

- **glucocorticoids**
  - reduce birth weight
  - alter organ maturation
  - cause hypertension, diabetes, depression, etc
  - Sex steroids ‘programme’

Prenatal glucocorticoid excess ‘programmes’ higher BP and glucose in adult offspring





Single dose of betamethasone 'programmes' insulin resistance 30 years later: Lancet 28th May 2005

Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial

Lancet 2005; 365: 1856–62

Stuart R Dalziel, Natalie K Walker, Varsha Parag, Colin Mantell, Harold H Rea, Anthony Rodgers, Jane E Harding

Clinical Trials Research Unit (S R Dalziel MBChB, H K Walker PhD, V Parag MSc, A Rodgers FAFPHM), Liggins Institute (S R Dalziel, Prof J E Harding FRACP), Division of Maori and Pacific Health (Prof C Mantell FRANZCOG), and Department of Medicine (Prof H H Rea FRACP), University of Auckland, Auckland, New Zealand

Correspondence to: Prof Jane Harding, Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand
j.harding@auckland.ac.nz

Summary

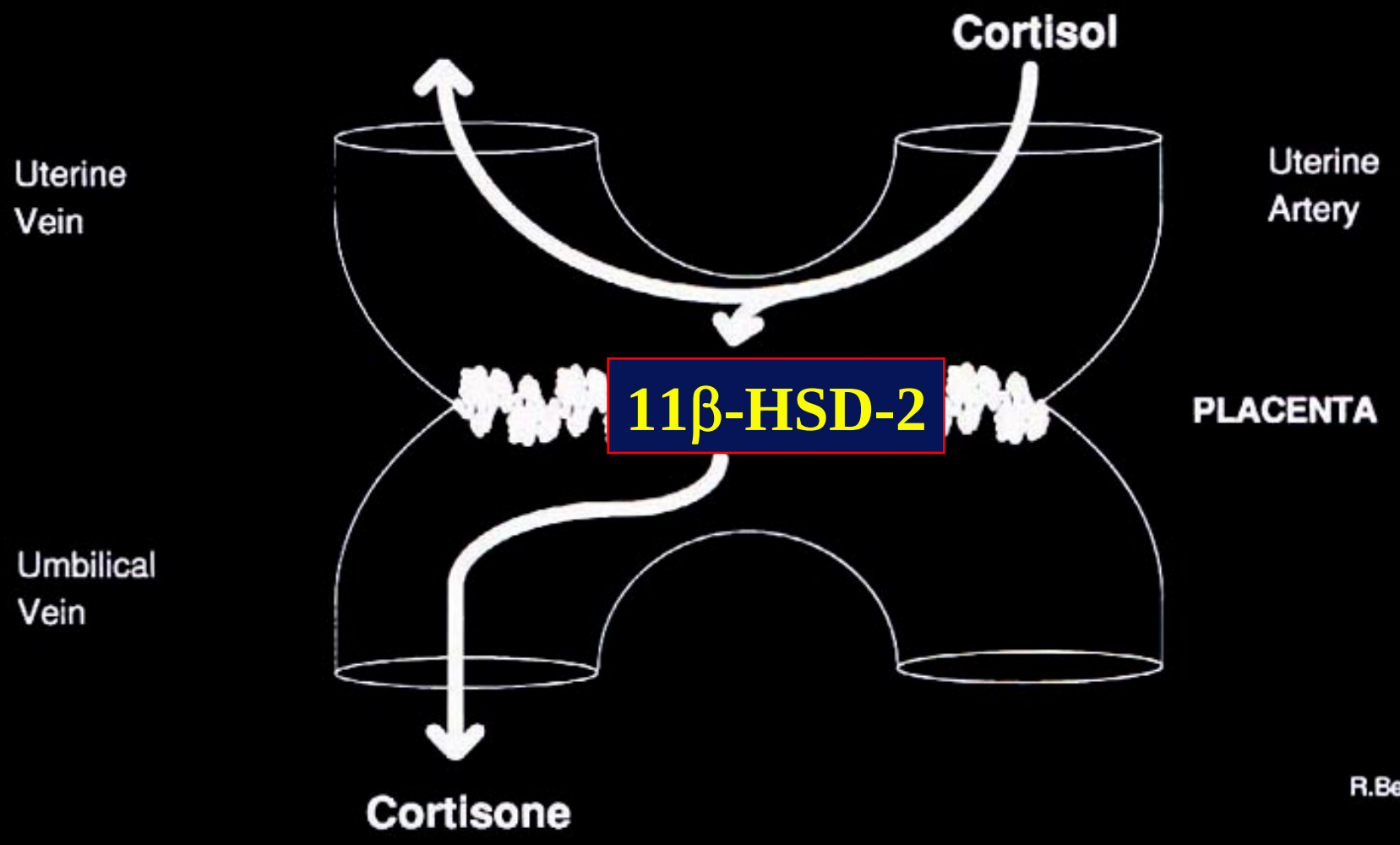
Background Antenatal betamethasone treatment is widely used for the prevention of neonatal respiratory distress syndrome in preterm infants and substantially reduces neonatal mortality and morbidity. Fetal exposure to excess glucocorticoids has been proposed as one of the core mechanisms of the fetal origins of adult disease hypothesis. We assessed whether antenatal exposure to betamethasone for the prevention of neonatal respiratory distress syndrome affects cardiovascular risk factors at 30 years of age.

Methods We followed up at age 30 years 534 individuals whose mothers participated in a double-blind, placebo-controlled, randomised trial of antenatal betamethasone for the prevention of neonatal respiratory distress syndrome. Mothers received two doses of betamethasone or placebo given by intramuscular injection 24 h apart. Follow-up assessments included anthropometry; measurement of blood pressure, blood lipids (after overnight fasting), and early morning cortisol levels; and a 75 g oral glucose tolerance test.

Findings There were no differences between those exposed to betamethasone and to placebo in body size, blood lipids, blood pressure, plasma cortisol, prevalence of diabetes, or history of cardiovascular disease. After a 75 g oral glucose tolerance test, participants exposed to betamethasone had higher plasma insulin concentrations at 30 min (60·5 *vs* 52·0 mIU/L; ratio of geometric means 1·16 [95% CI 1·03 to 1·31], p=0·02) and lower glucose concentrations at 120 min (4·8 *vs* 5·1 mmol/L; difference −0·26 mmol/L [−0·53 to 0·00], p=0·05) than did those exposed to placebo.

Interpretation Antenatal exposure to betamethasone might result in insulin resistance in adult offspring, but has no clinical effect on cardiovascular risk factors at 30 years of age. Thus, obstetricians should continue to use a single course of antenatal betamethasone for the prevention of neonatal respiratory distress syndrome.

Placental 11ß-hydroxysteroid dehydrogenase protects the foetus from maternal glucocorticoids



VOL 341: FEB 6, 1993

THE LANCET

HYPOTHESIS

Dysfunction of placental glucocorticoid barrier: link between fetal environment and adult hypertension?

CHRISTOPHER R. W. EDWARDS RAFN BENEDIKTSSON ROBERT S. LINDSAY JONATHAN R. SECKL

Birthweight is associated with the subsequent development of common disorders of adult life, especially hypertensior;:' maternal malnutrition has been suggested as the cause. We suggest an alternative aetiology-increased fetal exposure to maternal glucocorticoids. This hypothesis is supported by our findings that in rats decreased activity of the enzyme that acts as a placental barrier to maternal glucocorticoids (11~-hydroxysteroid dehydrogenase) is associated with low birthweight Furthermore, increased exposure of the fetus to exogenous glucocorticoids leads to low birthweight and subsequent hypertension in the offspring. Glucocorticoids acting during critical periods of prenatal development may, like other steroid hormones, exert organisational effects or imprint patterns of response that persist throughout life. Thus, the lifetime risk of common disorders may be partly determined by the intrauterine environment

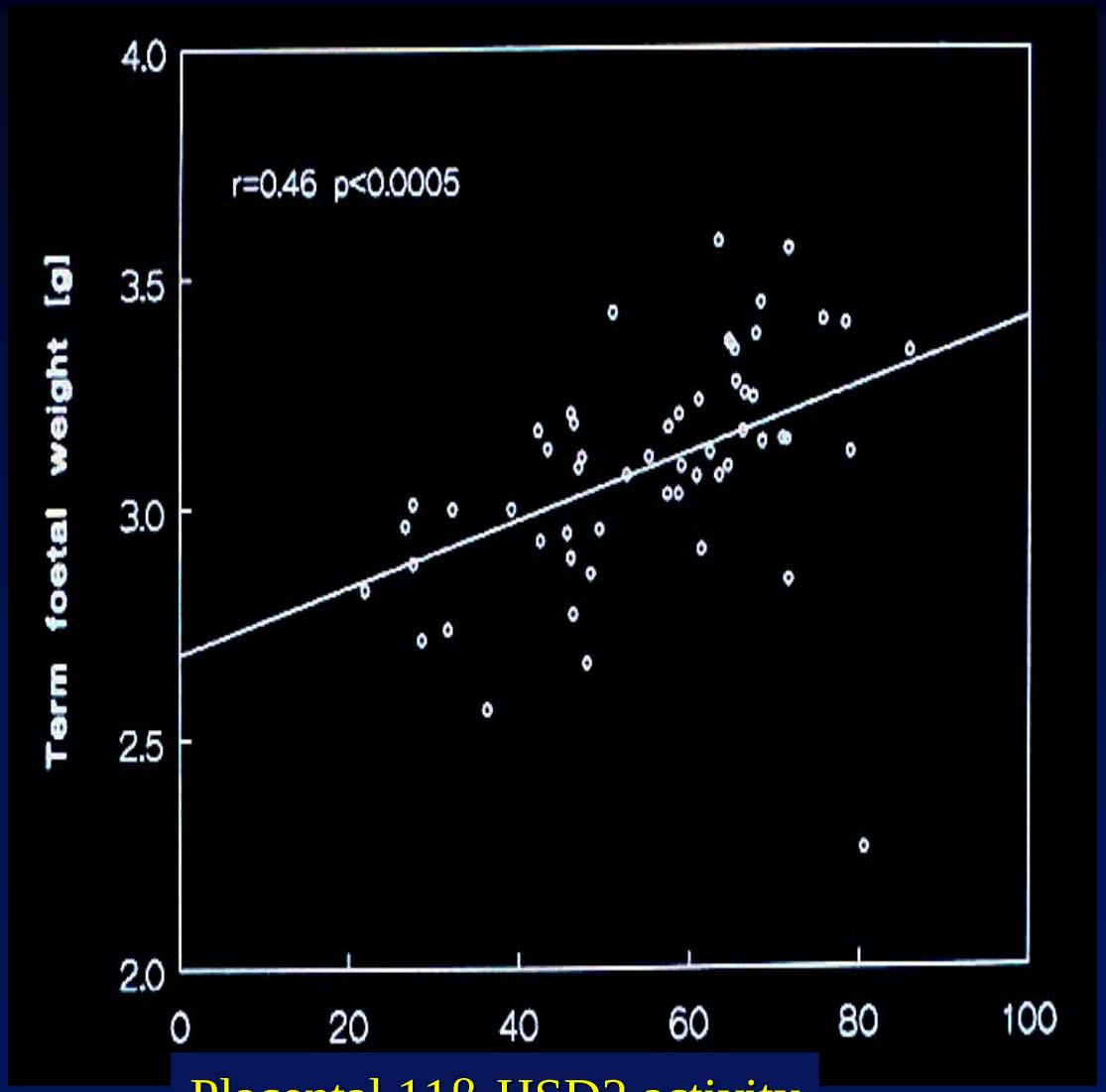
Lancet 1993; 341: 355-57.

whereas weight at 12 months correlates closely with weight subsequently. to This fInding suggests that in both animals and man there are local maternal factors, quite distinct from the maternal and paternal genes affecting the infant's ultimate size, which limit the growth of the fetus. Physical limitation of uterine space is not an important factor in rabbits,9 although the evidence in man is less clear.5 Whatever these maternal factors are, there could be catch-up growth after birth. It is interesting that adolescents with the highest blood pressures are those who grow fastest as children.ll

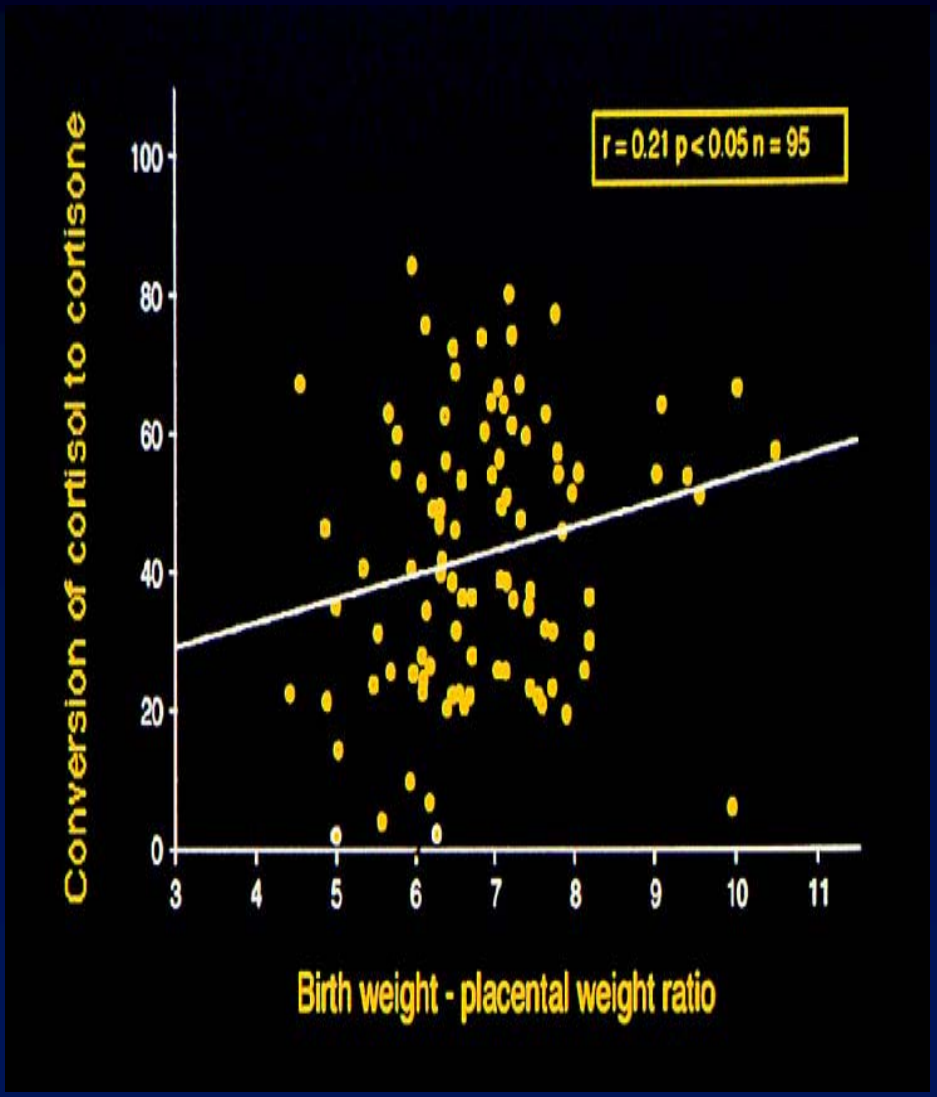
There are clear geographical differences in the incidence of cardiovascular disease in the UK; the correlation between these variations and blood pressure,12 suggests that there are important environmental determinants of blood pressure. Maternal smoking can affect fetal growth, but not placental weight.14 Moreover, smoking is associated with proportional reductions in birthweight and length, 15for any birthweight, head circumference increased with placental weight, but body length decreased. The Preston investigators5 suggested that there might be diversion of blood away from the trunk

Deficiency of the placental cortisol barrier and reduced birth weight

rat

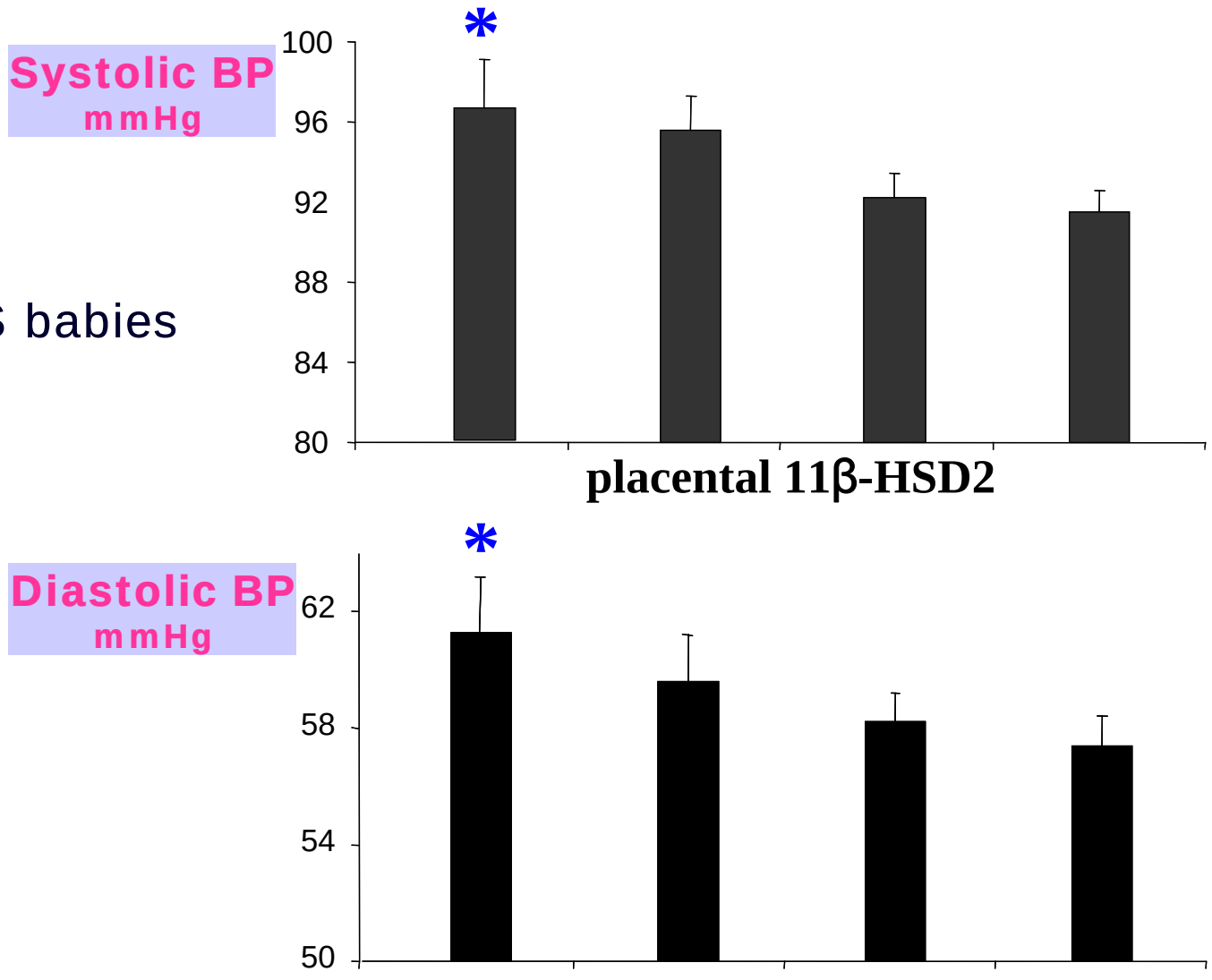


human



Placental 11β-HSD2 predicts BP at 3yrs

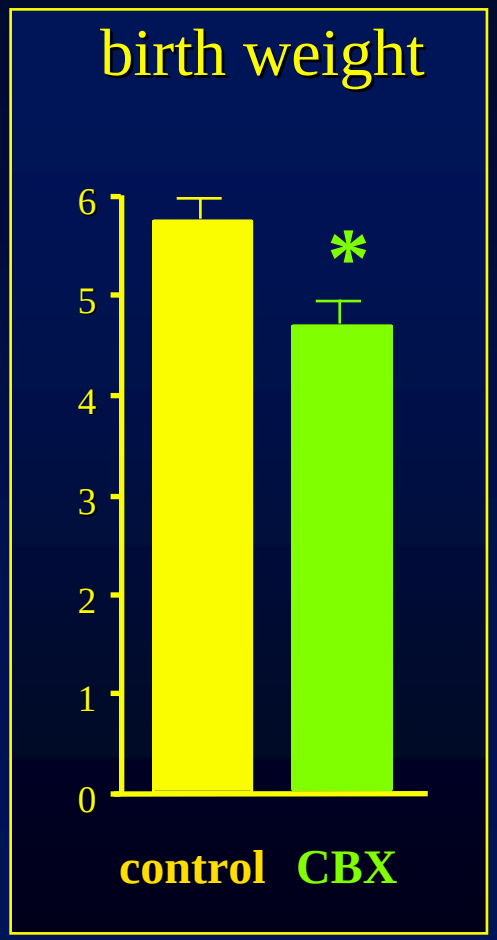
362 US babies



Huh et al, BMC Med 2008

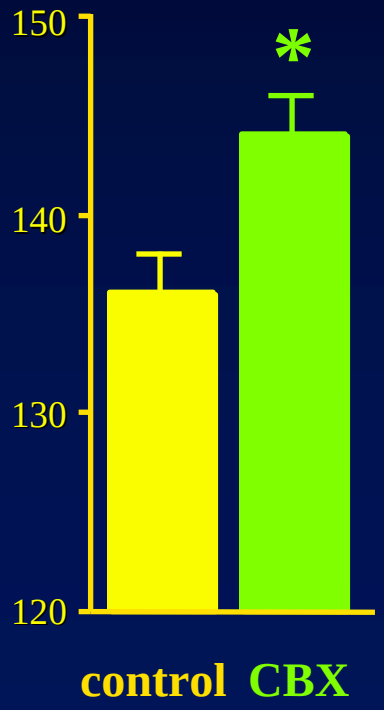

Bassett's
BEST BEFORE
(SEE TOP FLAP)
LIQUORICE
Allsorts
113 g 4 oz

11ß-HSD inhibition programmes increased blood pressure and glucose

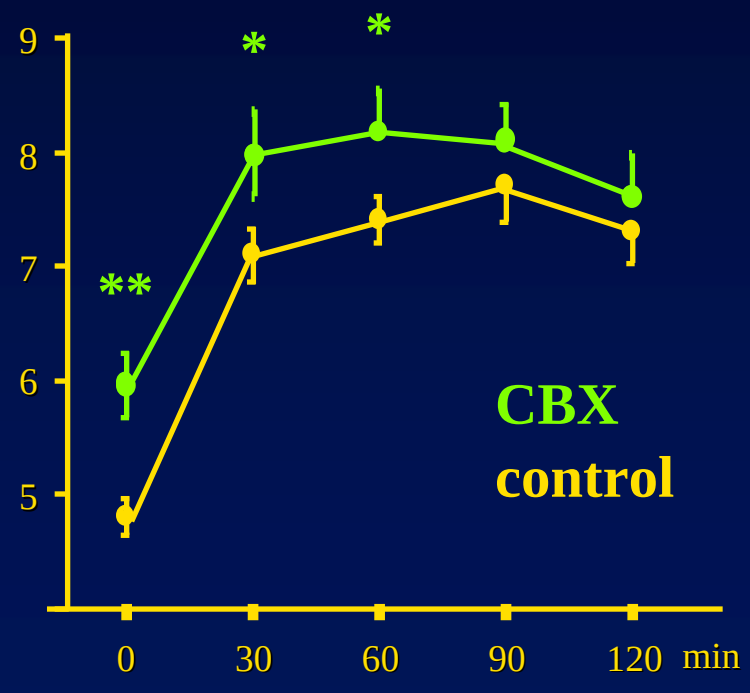


6 months →

blood pressure



blood glucose

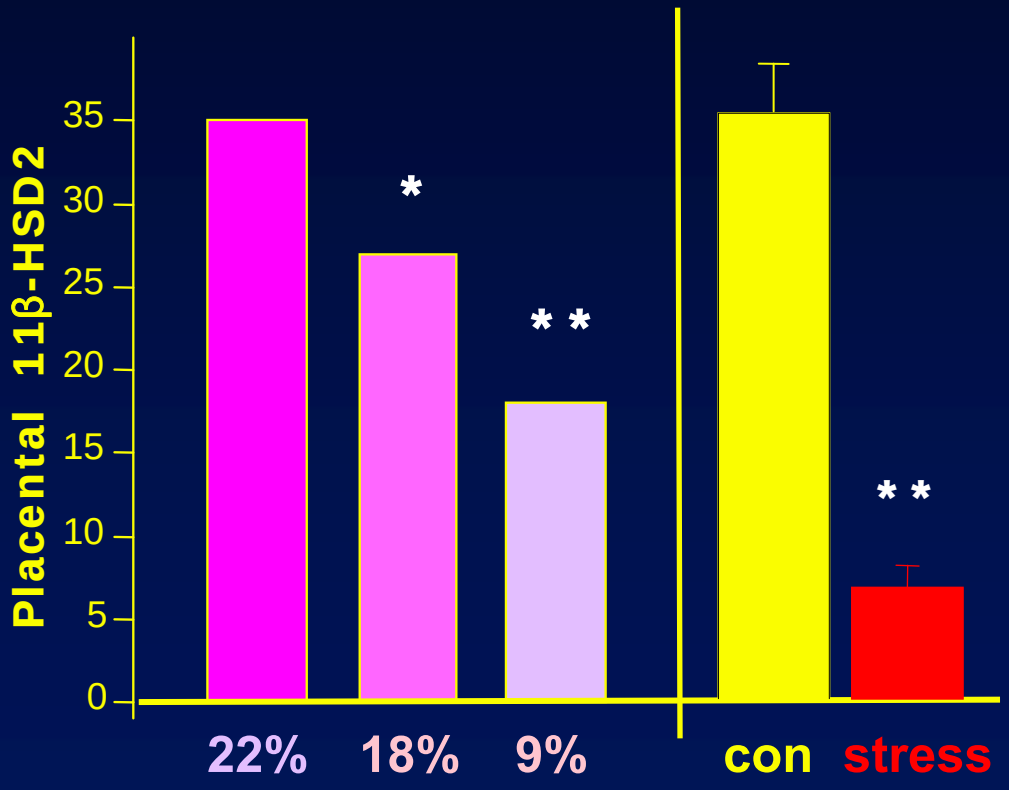


Lindsay et al, *Hypertension*, 1996
Lindsay et al, *Diabetologia*, 1996

Placental 11β-HSD2 deficiency: key to developmental programming?

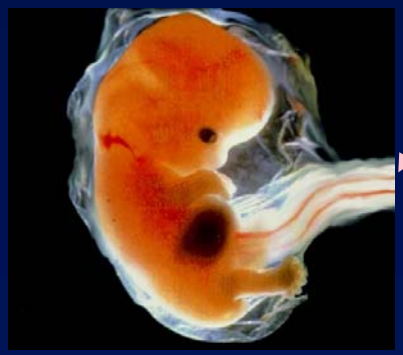
Protein restriction

stress



diet *stress* *disease*

Placental GC barrier

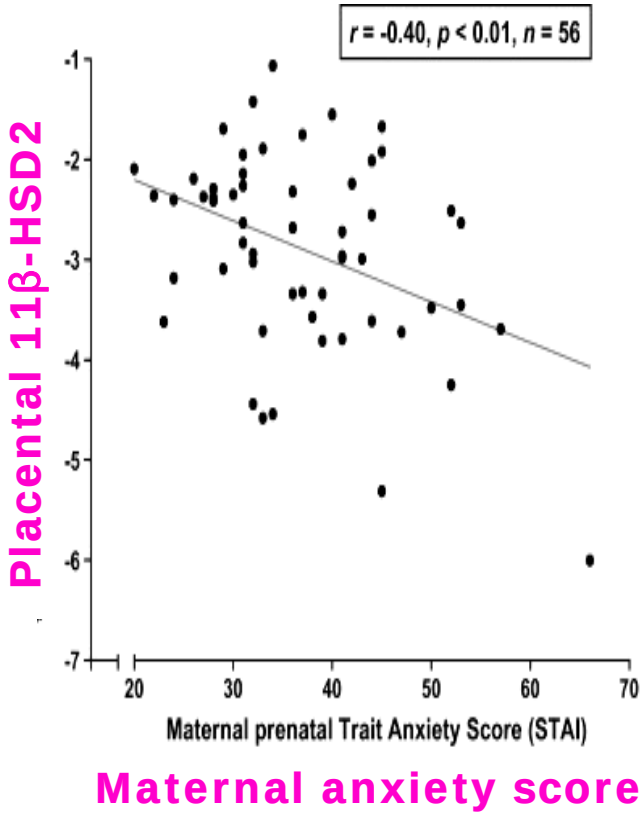


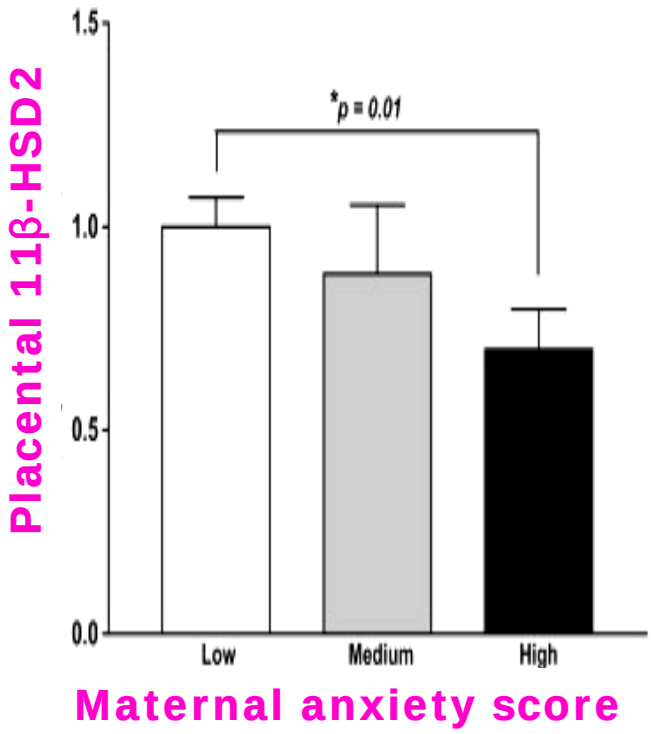
- *cort*
- *other placental and maternal factors*

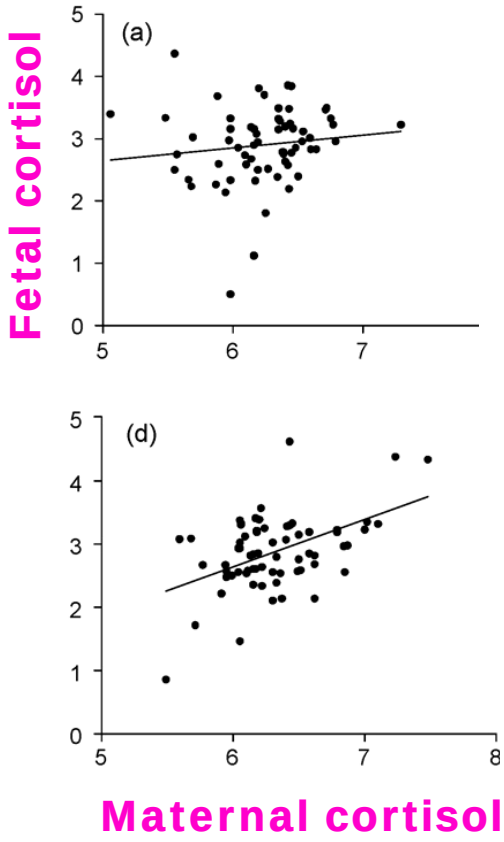
Langley-Evans et al, 1996

Mairesse et al, 2007

Maternal anxiety, reduced placental 11β-HSD2 and increased fetal cortisol







Glover, O'Donnell et al, Psychoneuroendocrinol, 2009; 2011

A Finnish favourite

Glycyrrhiza glabra

Maternal licorice consumption reduces offspring cognition and increases ADHD

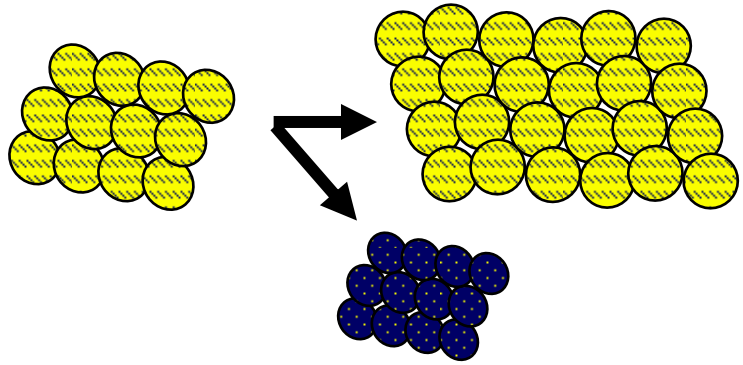
	Maternal consumption of glycyrrhizin		
	Zero-low	High	
	0-249 *N* = 202	≥ 500 mg/week *N* = 62	
	M (SD)	*M (SD)*	***P* value**
Wechsler Intelligence Scale for Children III			
Vocabulary	11.6 (3.0)	10.4 (2.8)	0.02
Similarities	11.6 (3.1)	10.2 (3.3)	0.01
Block design	10.9 (2.9)	9.8 (3.1)	0.04
Symbol search	10.8 (3.1)	10.3 (3.6)	0.46
Beery Development Visual-Motor Integration	102 (12.3)	99 (14.9)	0.23
Developmental Neuropsychological Assessment			
Narrative memory	10.4 (3.1)	9.3 (3.4)	0.04
Child Behavior Checklist			
Internalizing symptoms	50.4 (9.9)	52.7 (9.5)	0.13
Externalizing symptoms	50.1 (8.4)	53.6 (8.8)	0.03
Total behavior problems	49.1 (9.1)	53.2 (8.7)	0.01
Attention Deficit Hyperactivity Disorder	15.4 %	**25.9 %**	0.04

Effects persist after adjusting for……
child's sex, age, length of gestation, birth weight, head circumference, birth order,
mother's age, occupational status, smoking, alcohol consumption, psychological stress during pregnancy, mode of delivery, gestational diabetes, gestational hypertension and preeclampsia

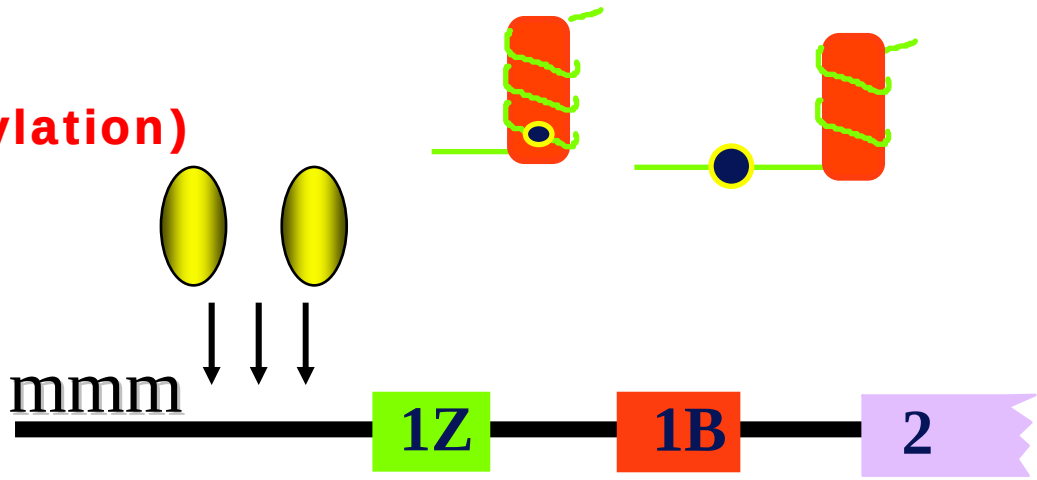
Räikkönen et al, Am J Epid 2010

How to programme a tissue?

- **alter cell number**
  - **proliferation**
  - **apoptosis**

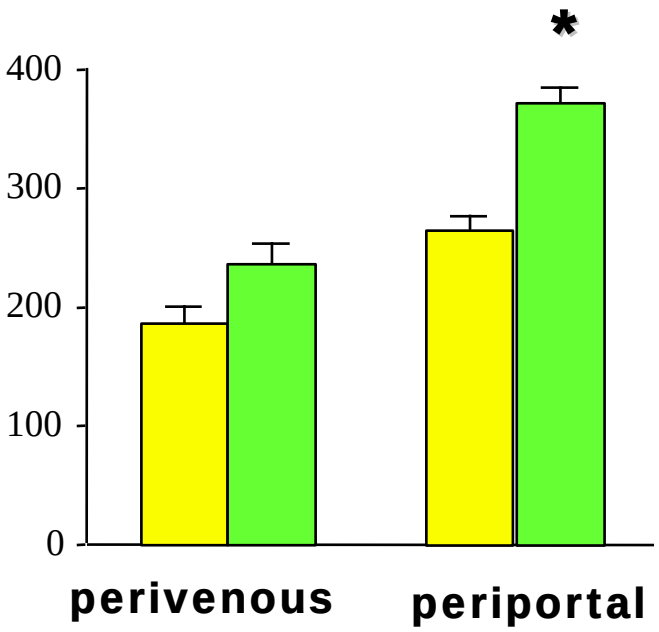


- **alter gene expression**
  - **chromatin**
    - **histones (acetylation, methylation)**
    - **DNA methylation**
  - **transcription factors**



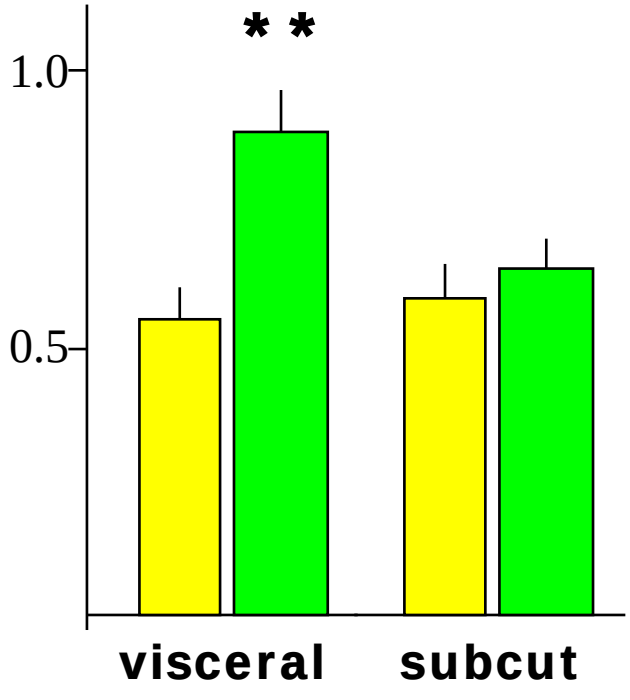
Prenatal challenges programme the glucocorticoid receptor, but in a cell-specific manner

liver



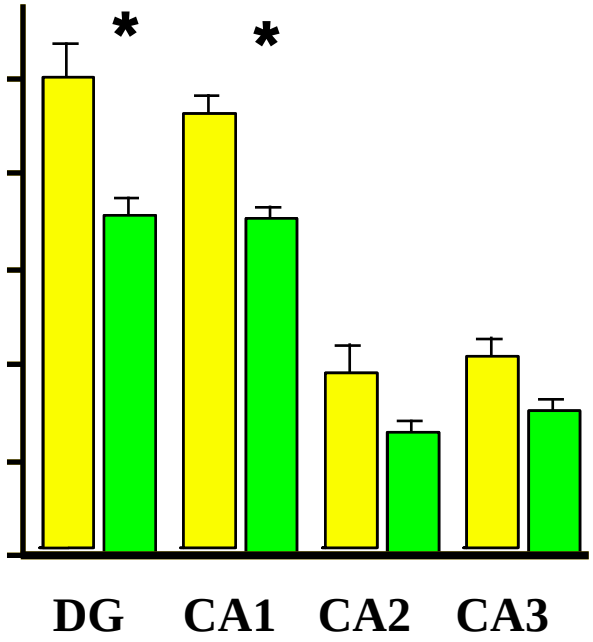
Nyirenda et al, JCI, 1998;

adipose



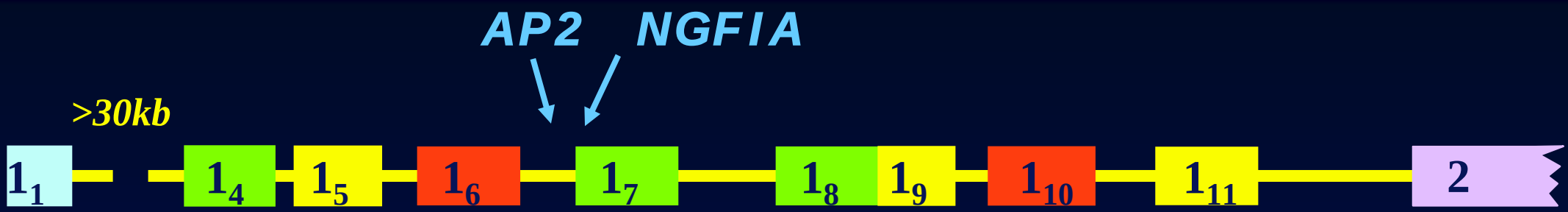
Cleasby et al, *Endo, 2003*

hippocampus



Levitt et al, *Neuroendocrinol*, 1996

The GR gene contains multiple alternate, tissue-specific 1st exons

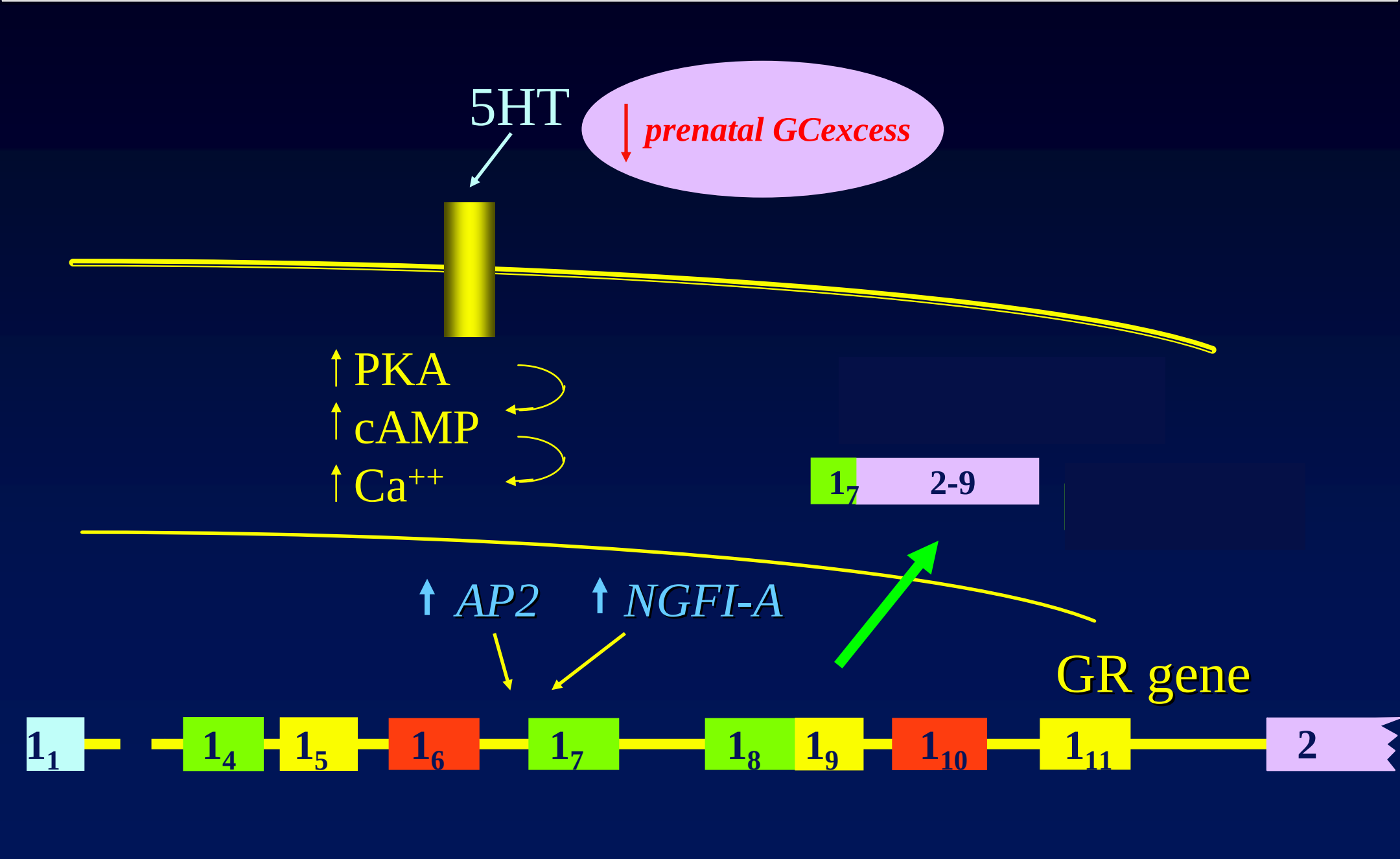


n >11

	liver	hippoc	thymus
1_6 2-9	+ + +	+ + +	+ + +
1_7 2-9	-	+ +	-
1_9 2-9	+ +	-	-
1_1 2-9	-	-	+ +

McCormick et al, Mol Endo, 2000

5HT regulates hippocampal GR gene transcription



How can early life events affect someone for the rest of their lifespan?

epigenetics

epigenetics

sub-group *Cactornis*, lately brought from Bow island, in the Low Archipelago. Of *Cactornis*, the two species may be often seen climbing about the flowers of the great cactus trees; but all the other species of this group of finches, mingled together in flocks, feed on the dry and sterile ground of the lower districts. The males of all, or certainly of the greater number, are jet black; and the females (with perhaps one or two exceptions) are brown. The most curious fact is the perfect gradation in the size of the beaks in the different species of *Geospiza*, from one as large as that of a hawfinch to that of a chaffinch, and (if Mr Gould is right in including his sub-group, *Certhidea*, in the main group), even to that of a warbler. The largest beak in the genus *Geospiza* is shown in Fig. 1, and the smallest in Fig. 3; but instead of there being only one intermediate species, with a beak of the size shown in Fig. 2, there are no less than six species with insensibly graduated beaks. The beak of the sub-group *Certhidea*, is shown in Fig. 4. The beak of *Cactornis* is somewhat like that of a starling; and that of the fourth sub-group, *Camarhynchus*, is slightly parrot-shaped. Seeing this gradation and diversity of structure in one small, intimately related group of birds, one might really fancy that from an original paucity of birds in this archipelago, one species had been taken and modified for different ends. In a like manner it might

THE VOYAGE OF THE BEAGLE 361

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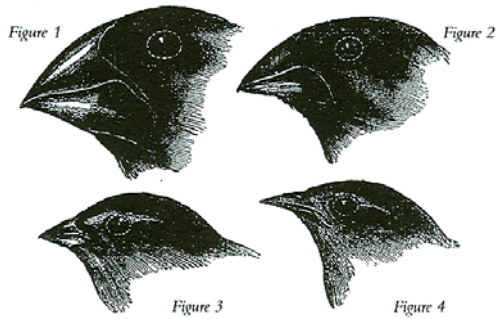
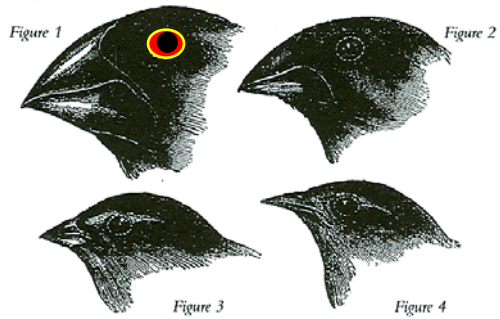


1 *Geospiza magnirostris* 2 *Geospiza fortis*
3 *Geospiza parvula* 4 *Certhidea olivacea*



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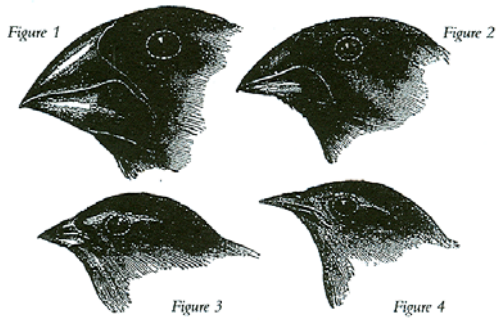

1 *Geospiza magnirostris* 2 *Geospiza fortis*
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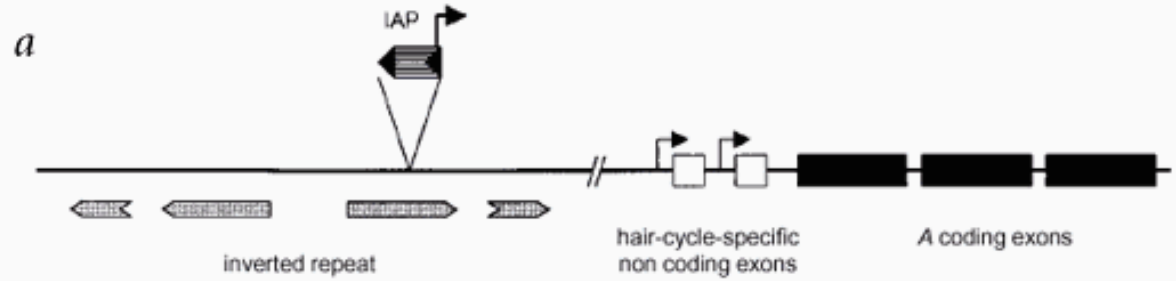
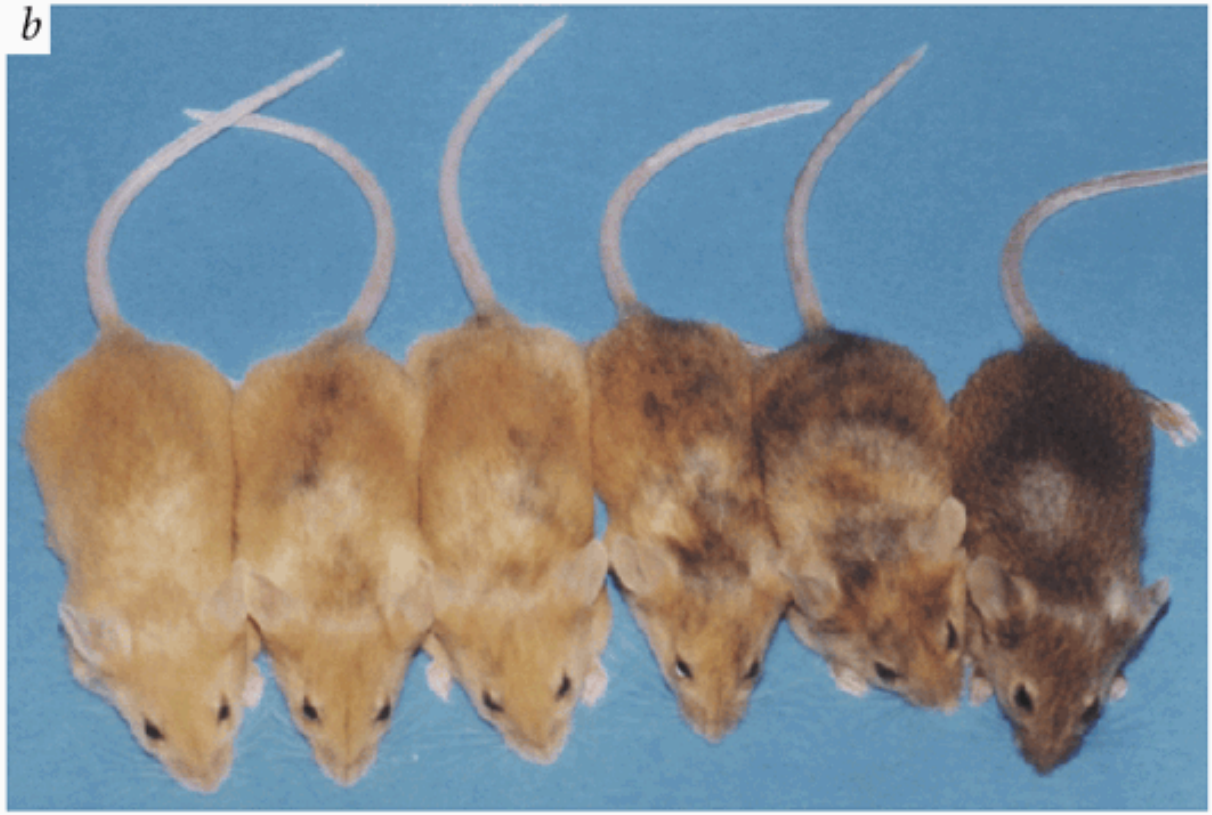

a
IAP
inverted repeat
hair-cycle-specific
non coding exons
A coding exons

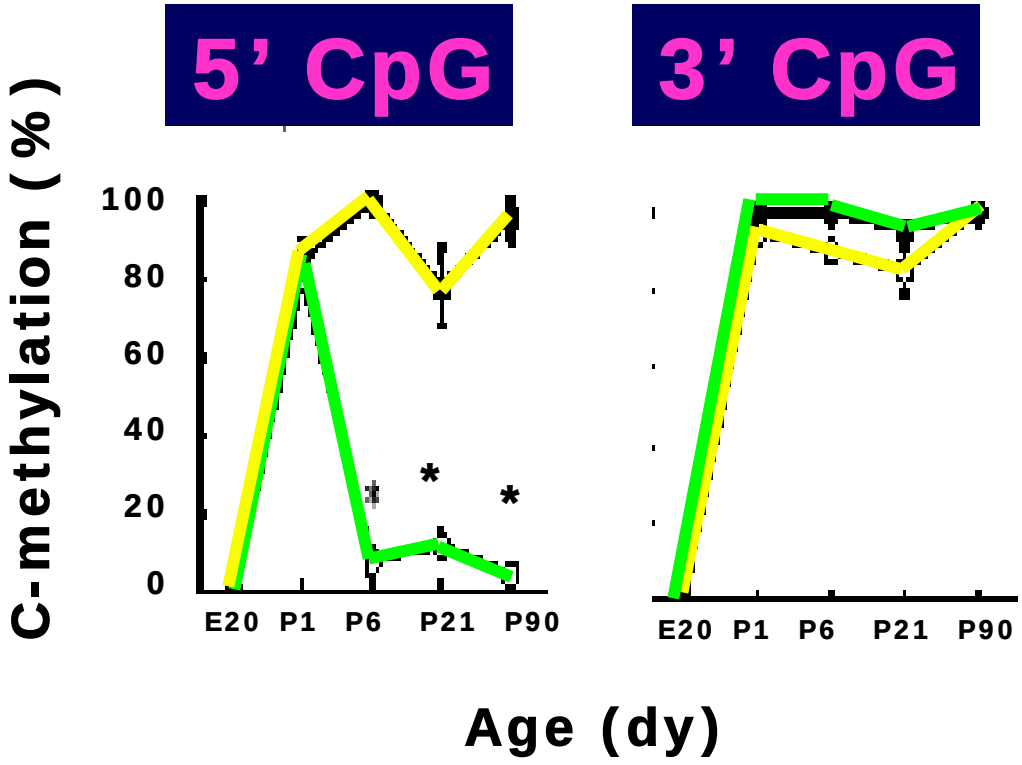

b

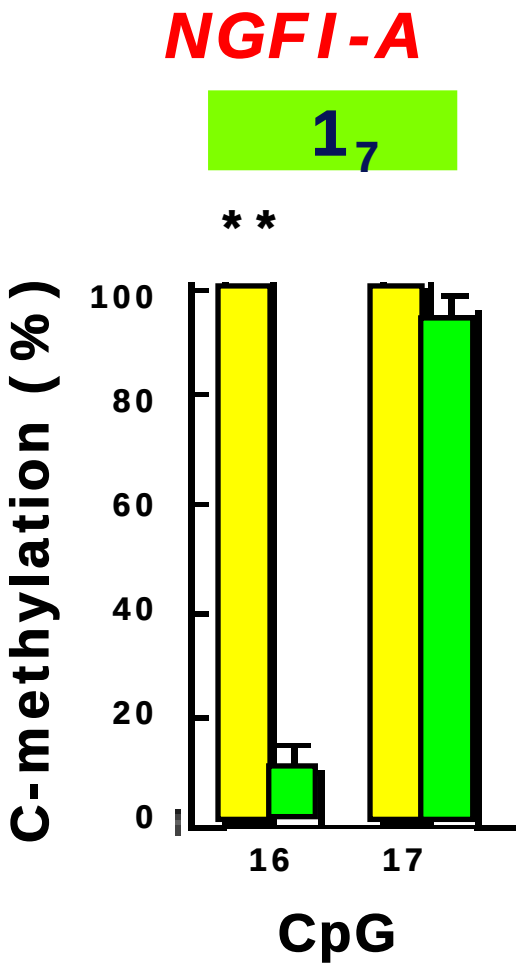
Epigenetics - the differences in genetically-identical individuals grown in different wombs

Copycat

Copycat's 'mum'

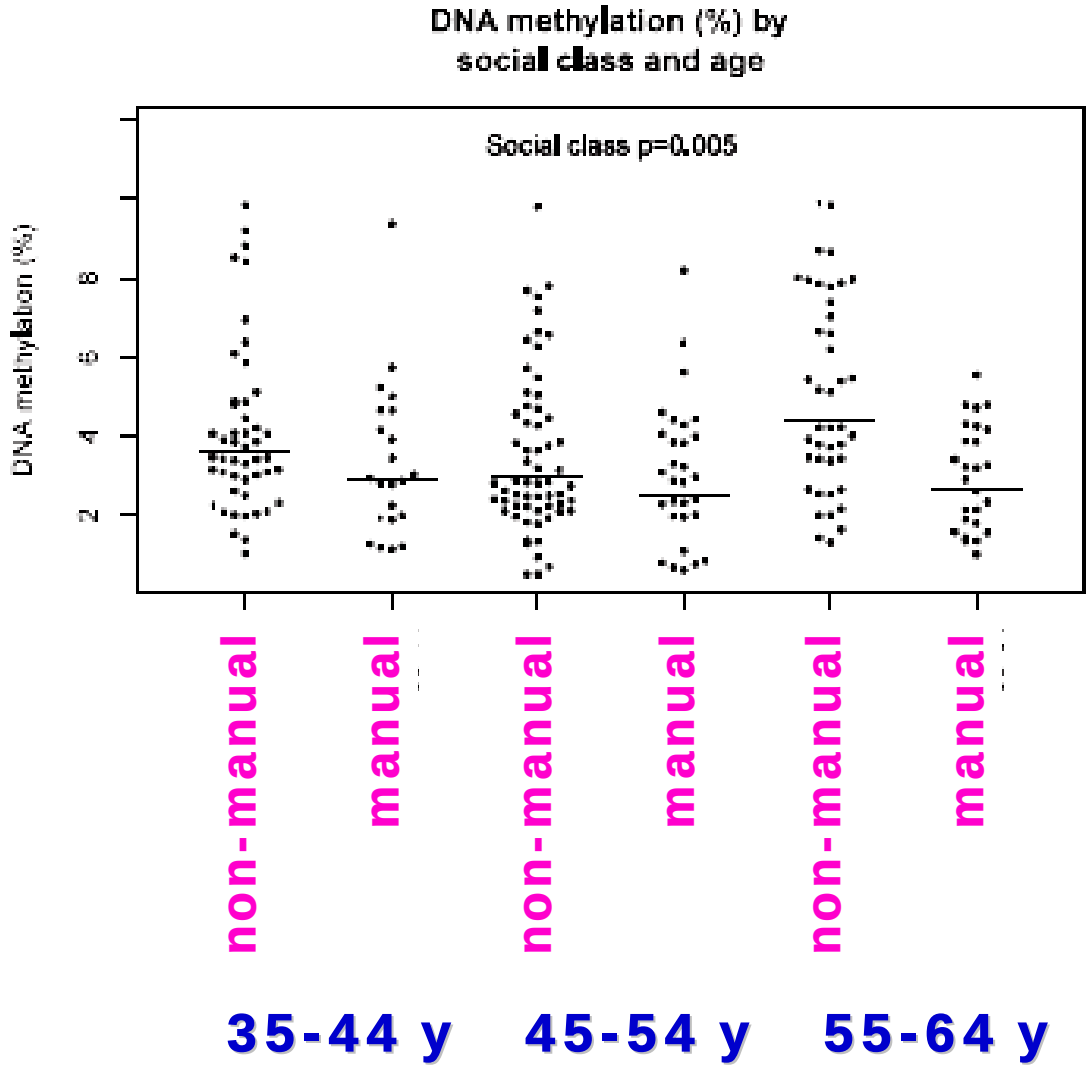
Early life environment determines the epigenetic state (methylation) of the GR 1$_7$ promoter





Weaver et al, Nature Neurosci 2004

Lower total DNA methylation with low SES



McGuinness et al, Int J Epidemiol 2012

The *excitement* of steroid metabolism

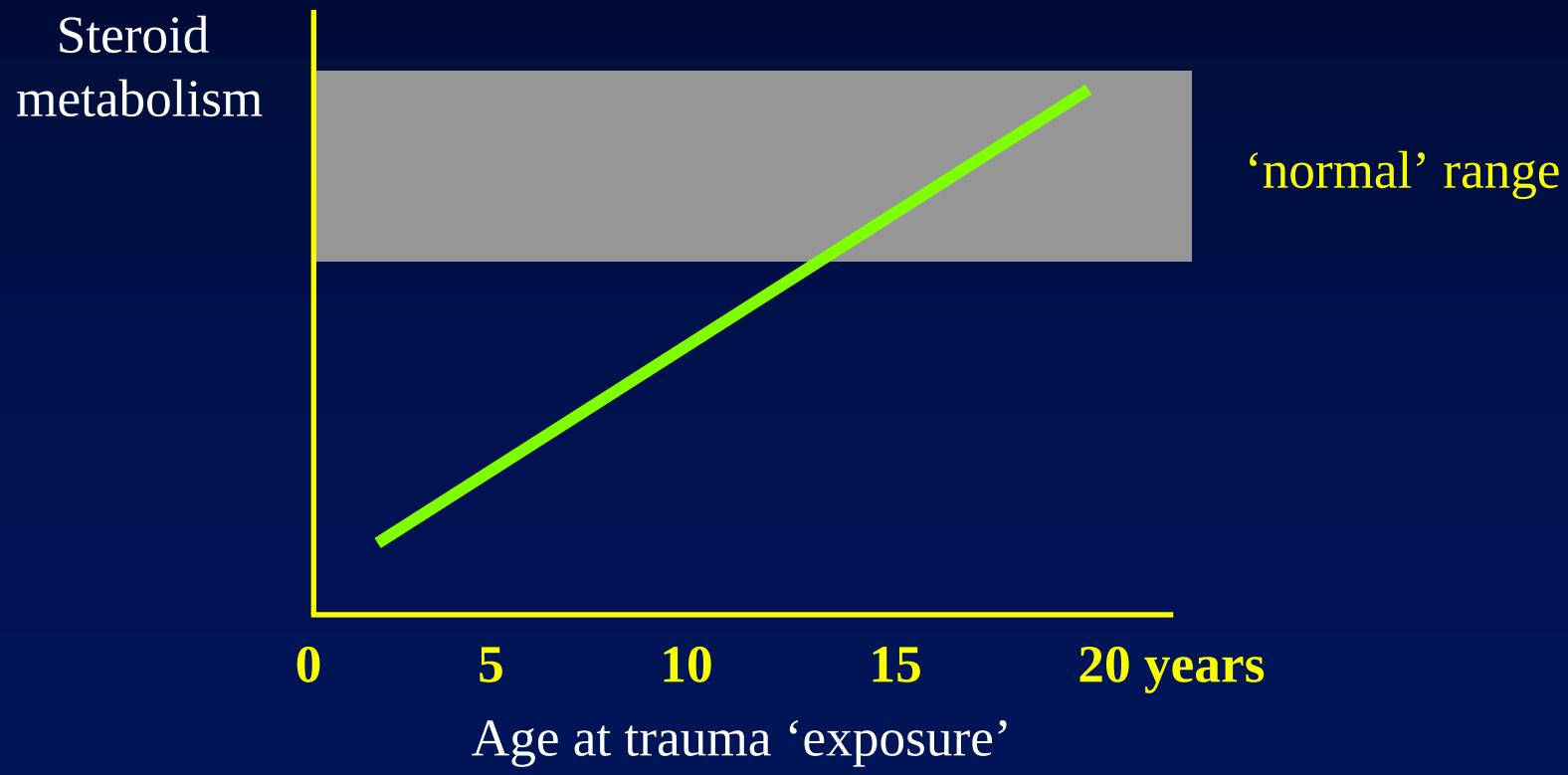
Children exposed to the Holocaust

Lower glucocorticoid metabolism in Holocaust survivors

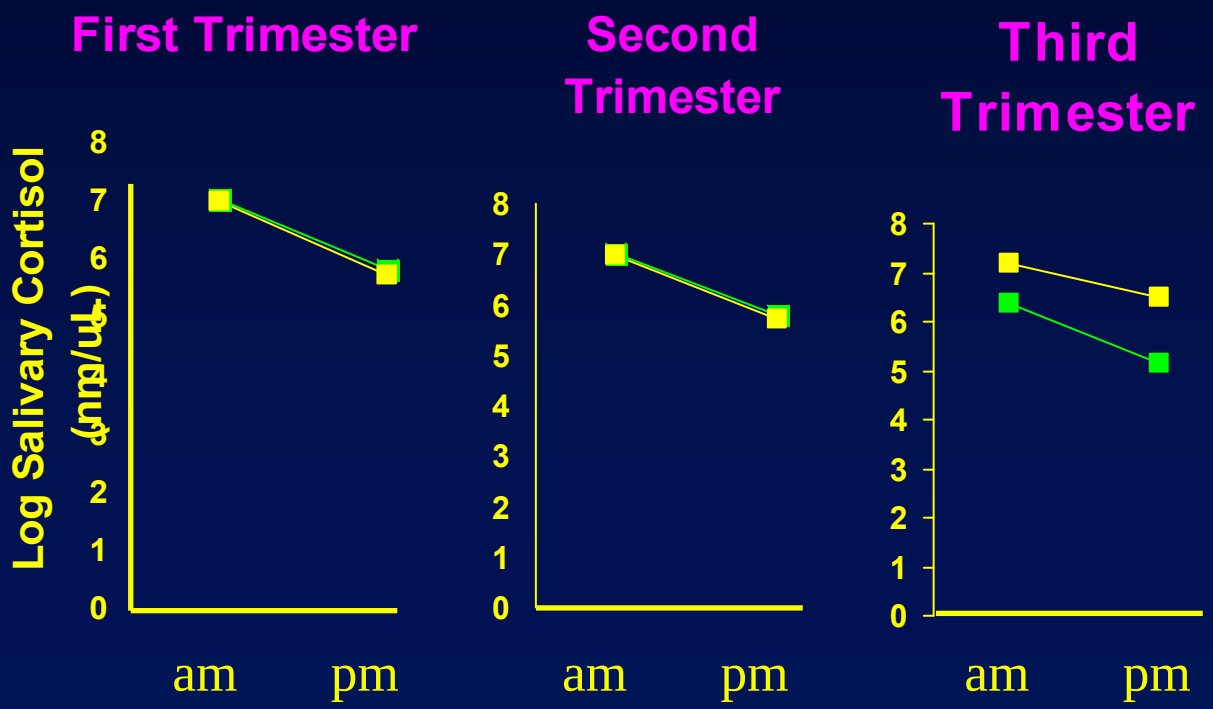
	Controls (n=22)	Holocaust survivors (n=51)
Total glucocorticoids	11000 ± 1200	6500 ± 600* ↓
5α-THF	5600 ± 600	2500 ± 400** ↓
5β-THF	1900 ± 400	1600 ± 300
5α-red ratio	17 ± 4	5.6 ± 0.7** ↓
5β-red ratio	8.0 ± 1.5	7.4 ± 1.4
11ß-HSD2 ratio	1.23 ± 0.08	0.99 ± 0.08** ↓

Yehuda et al, J Psychiatr Res 2009

Younger at trauma - greater decrease in metabolism



9.11 study - 1 yr old offspring cortisol altered: only after 3rd trimester exposure



Yehuda et al, *JCE&M*, 2005

INTRACRINE EFFECTS

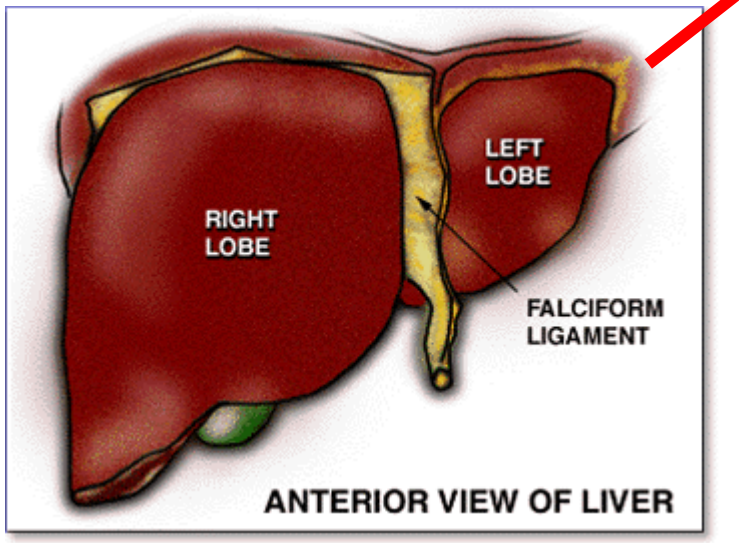
2 enzymes are reduced permanently in youngest exposed to Holocaust

11β-HSD2

cortisol ⇢ cortisone

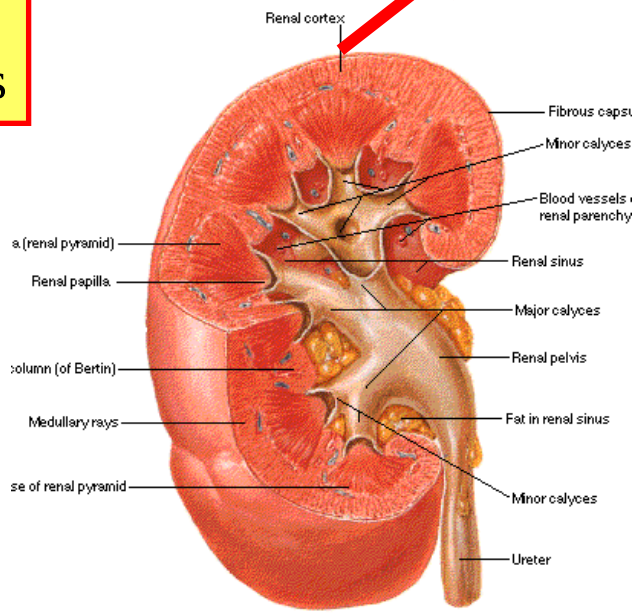
5α-reductase

5α-dihydrocortisol



Increased fuel
Glucose
Cholesterol and fats

Increased BP
Salt retention
Blood pressure



Both seem plausible early life adaptations to starvation/stress

Mismatch

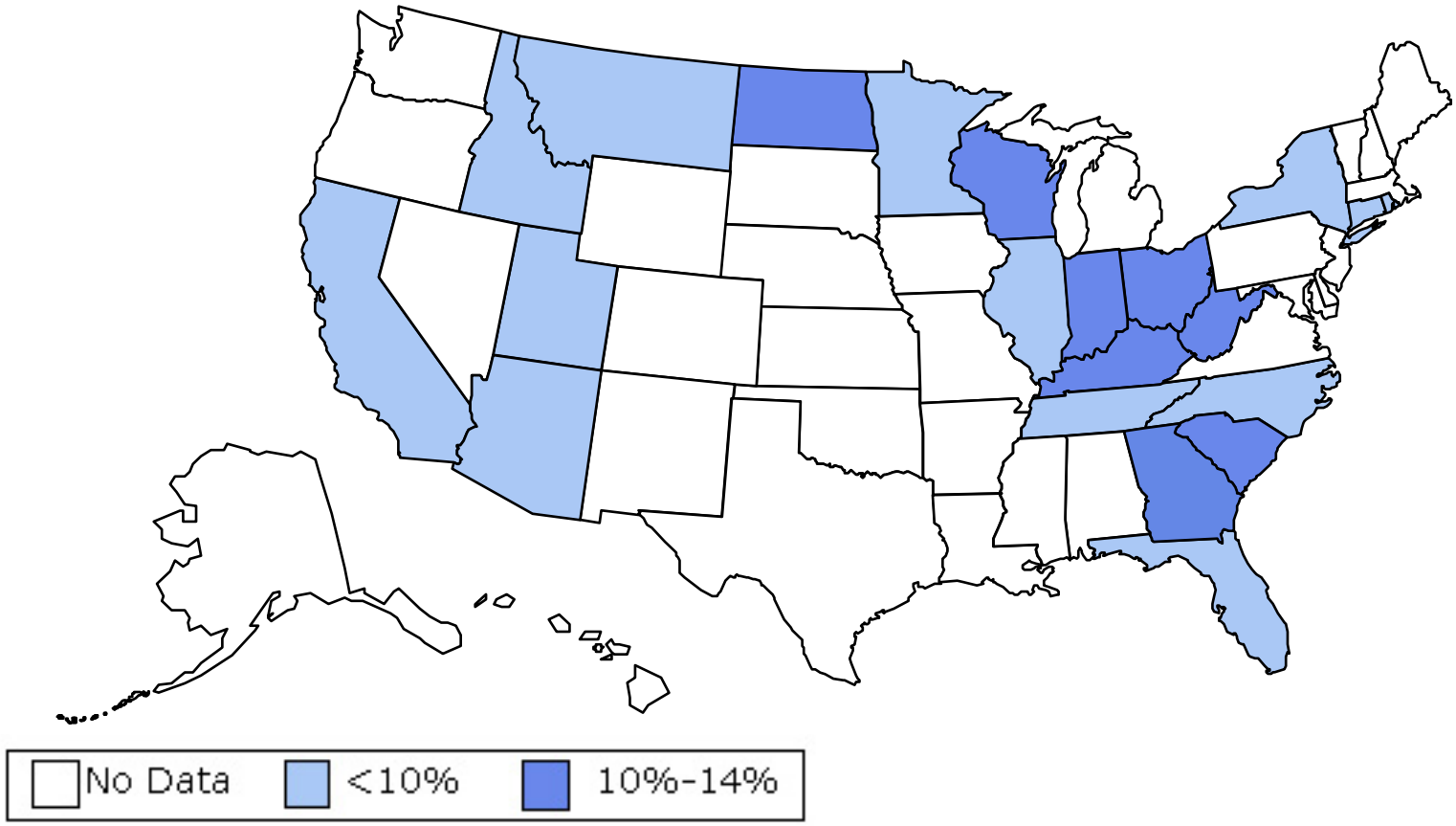
Programmed for deprivation… (famine, physical challenge)….

then born to
EXCESS and STRESS

Obesity Trends* Among U.S. Adults

BRFSS, 1985

(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)



CDC
SAFER·HEALTHIER·PEOPLE

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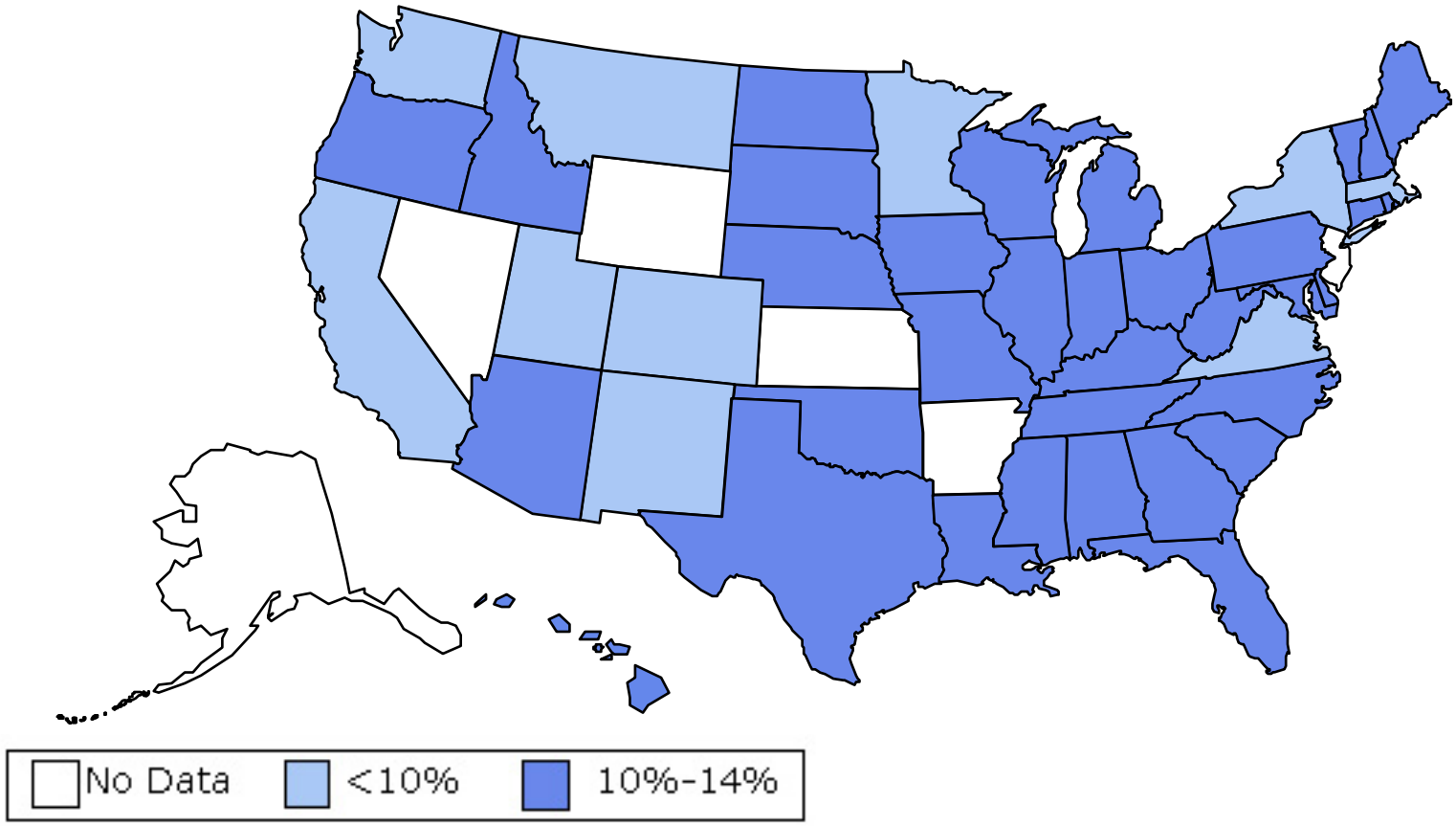

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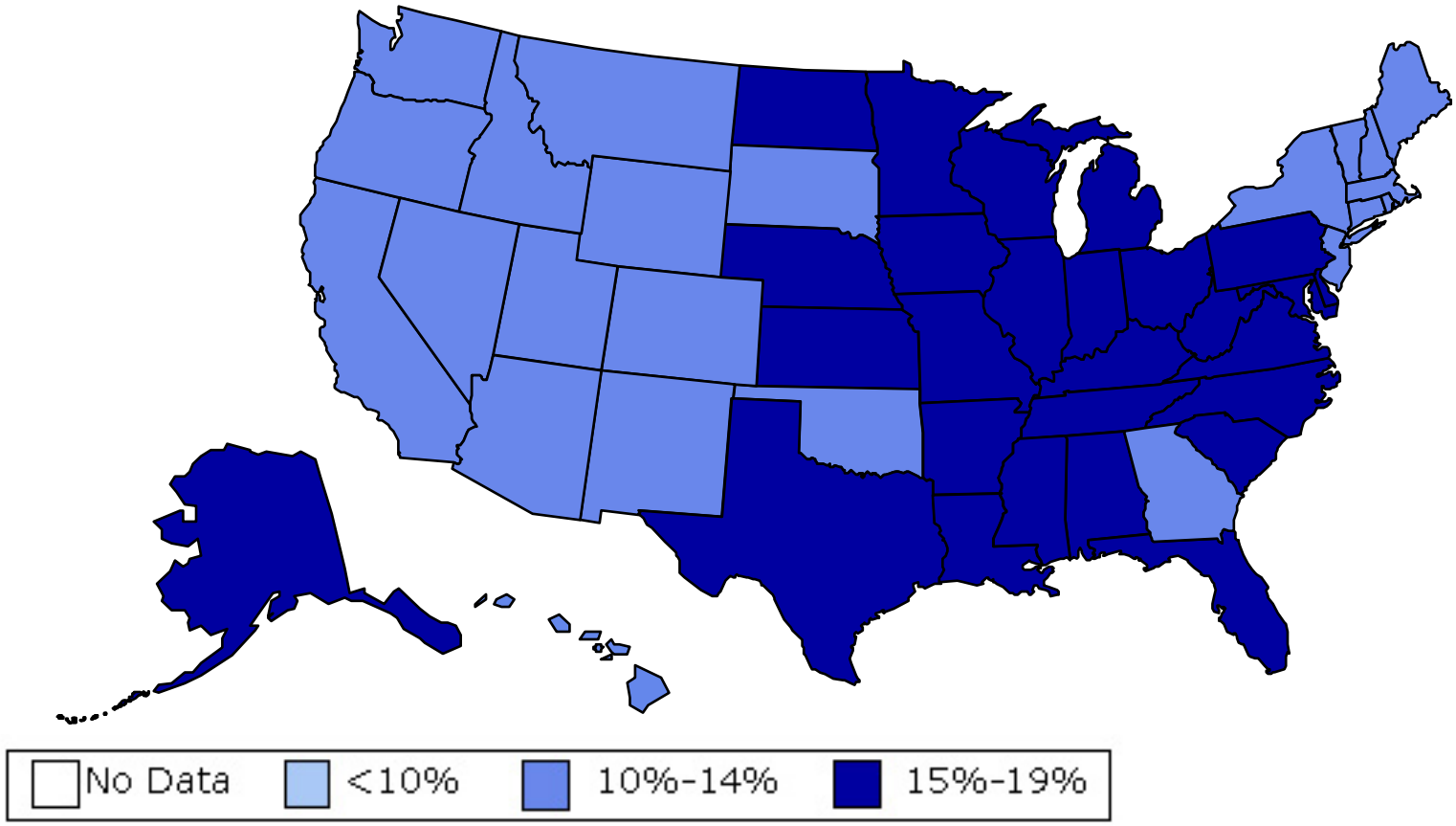

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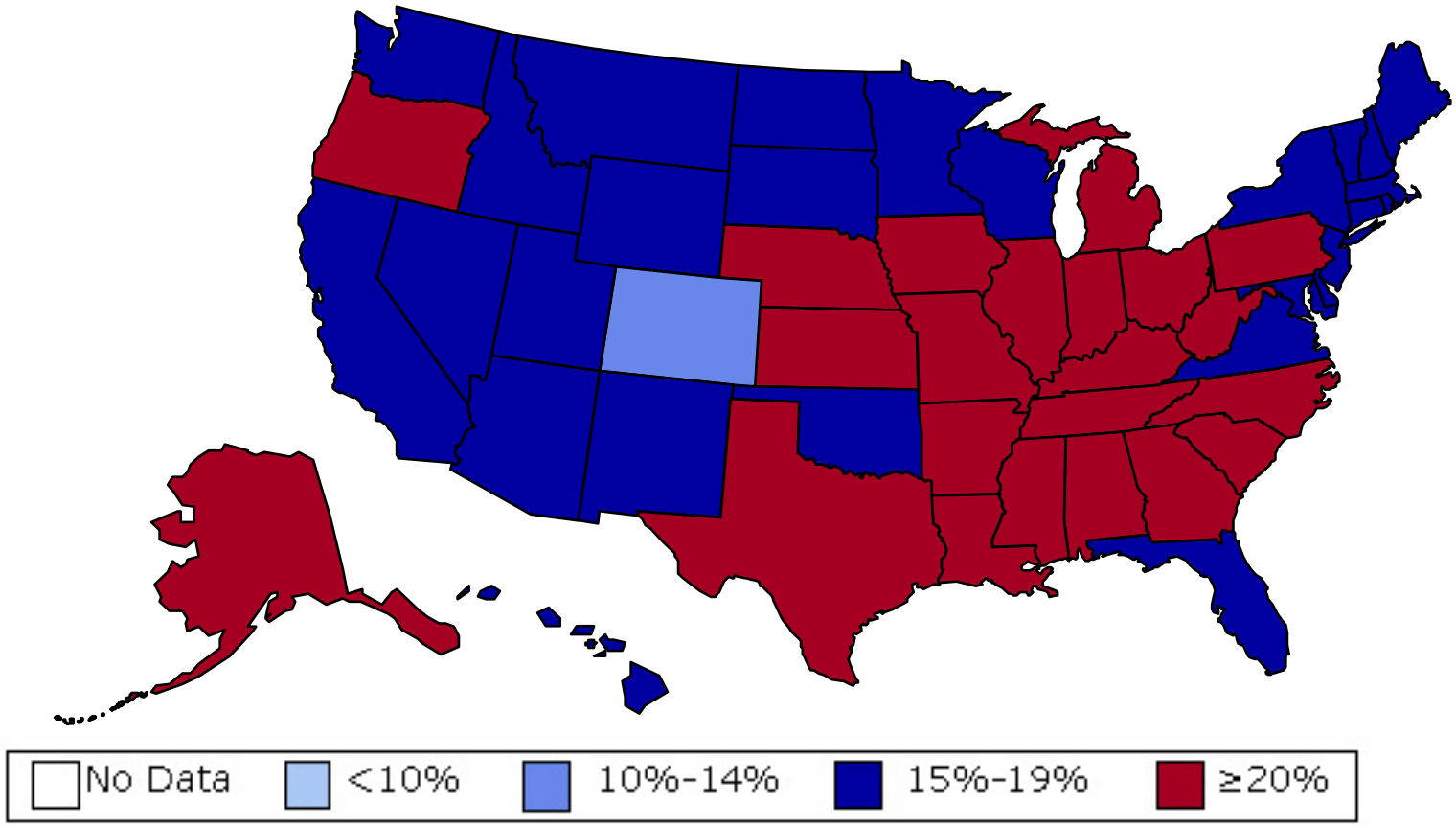

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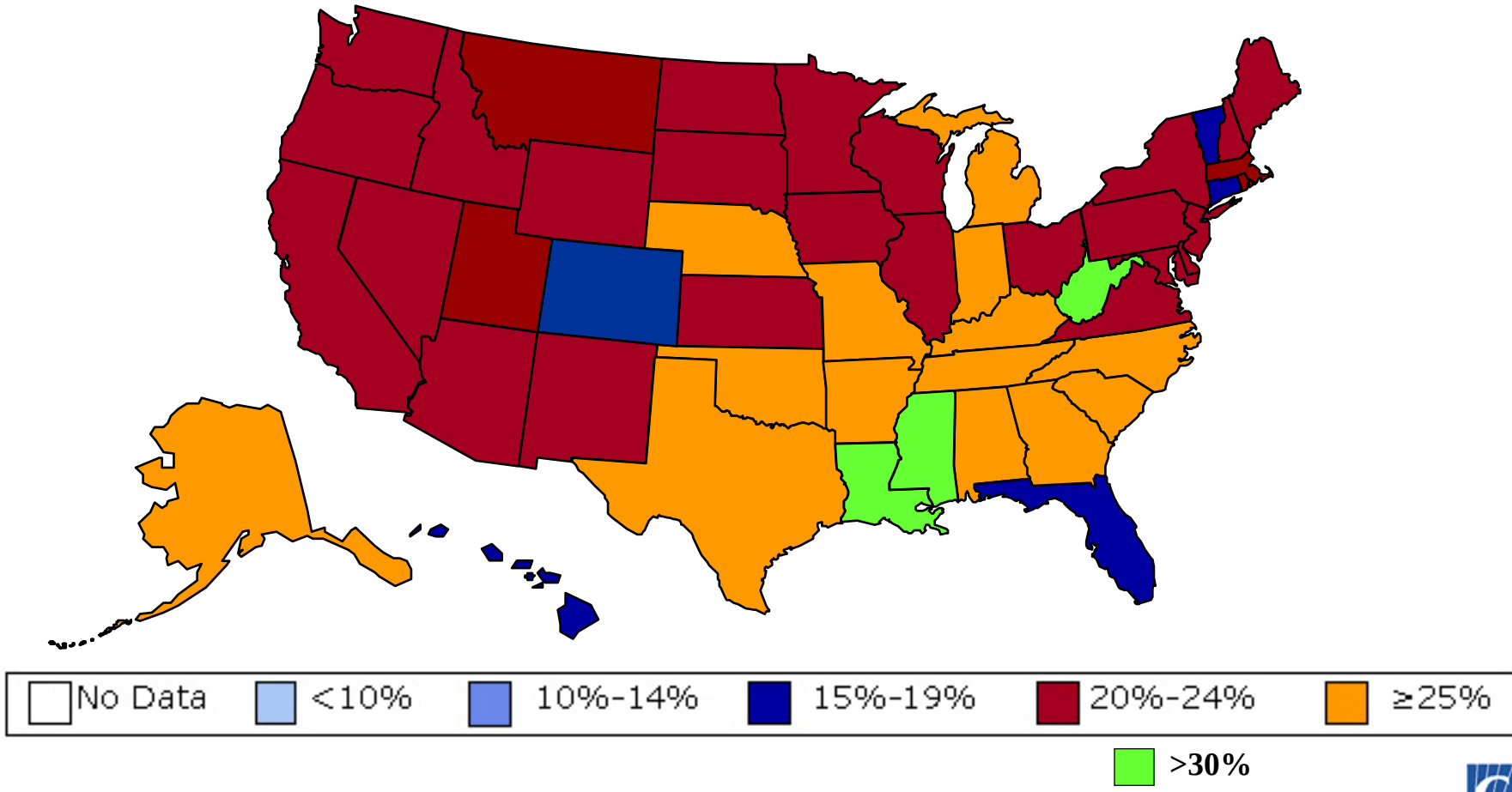

Obesity Trends* Among U.S. Adults

BRFSS, 2010

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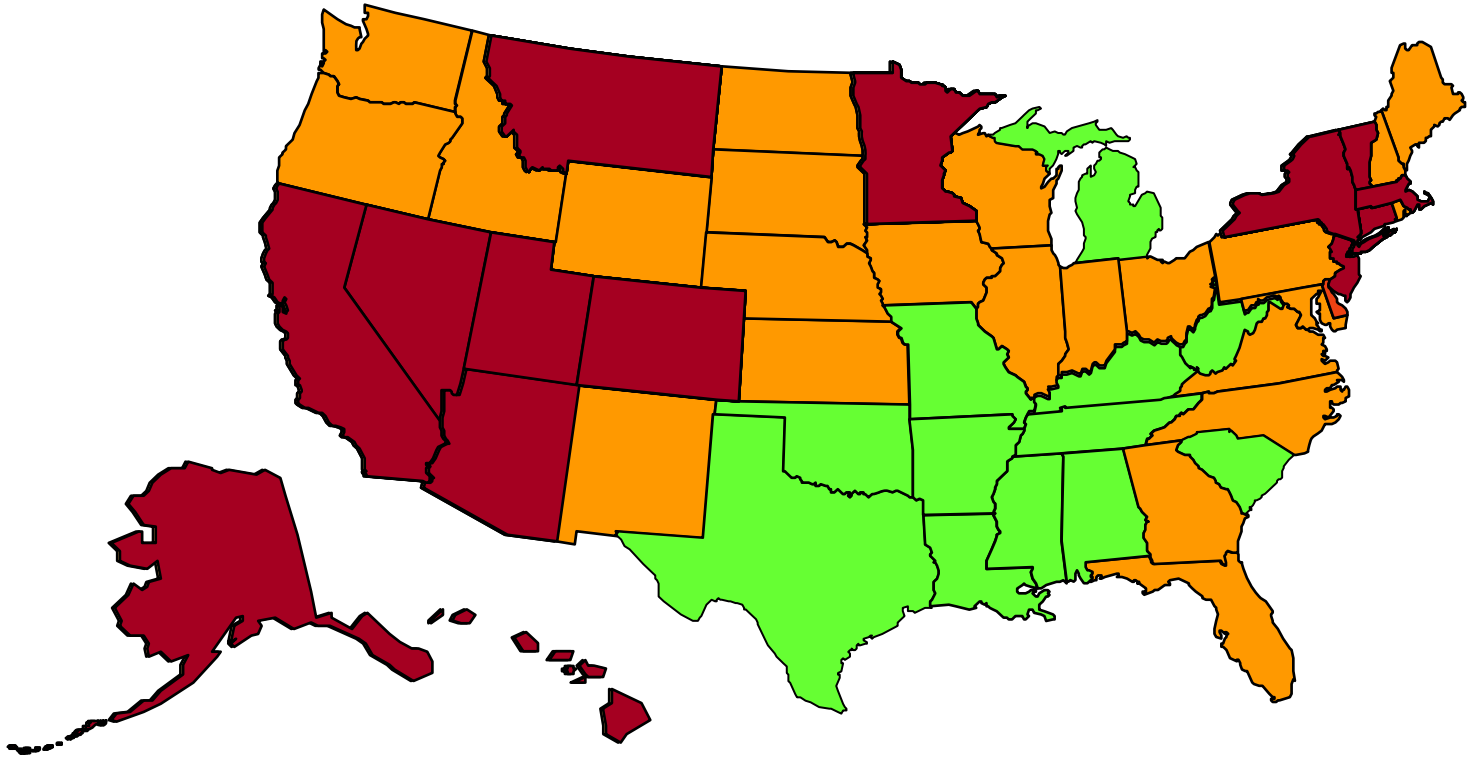
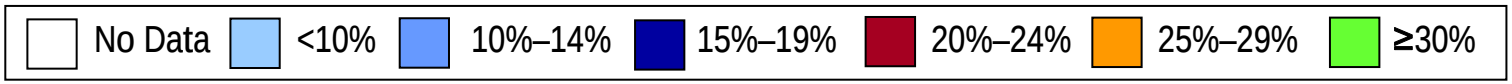
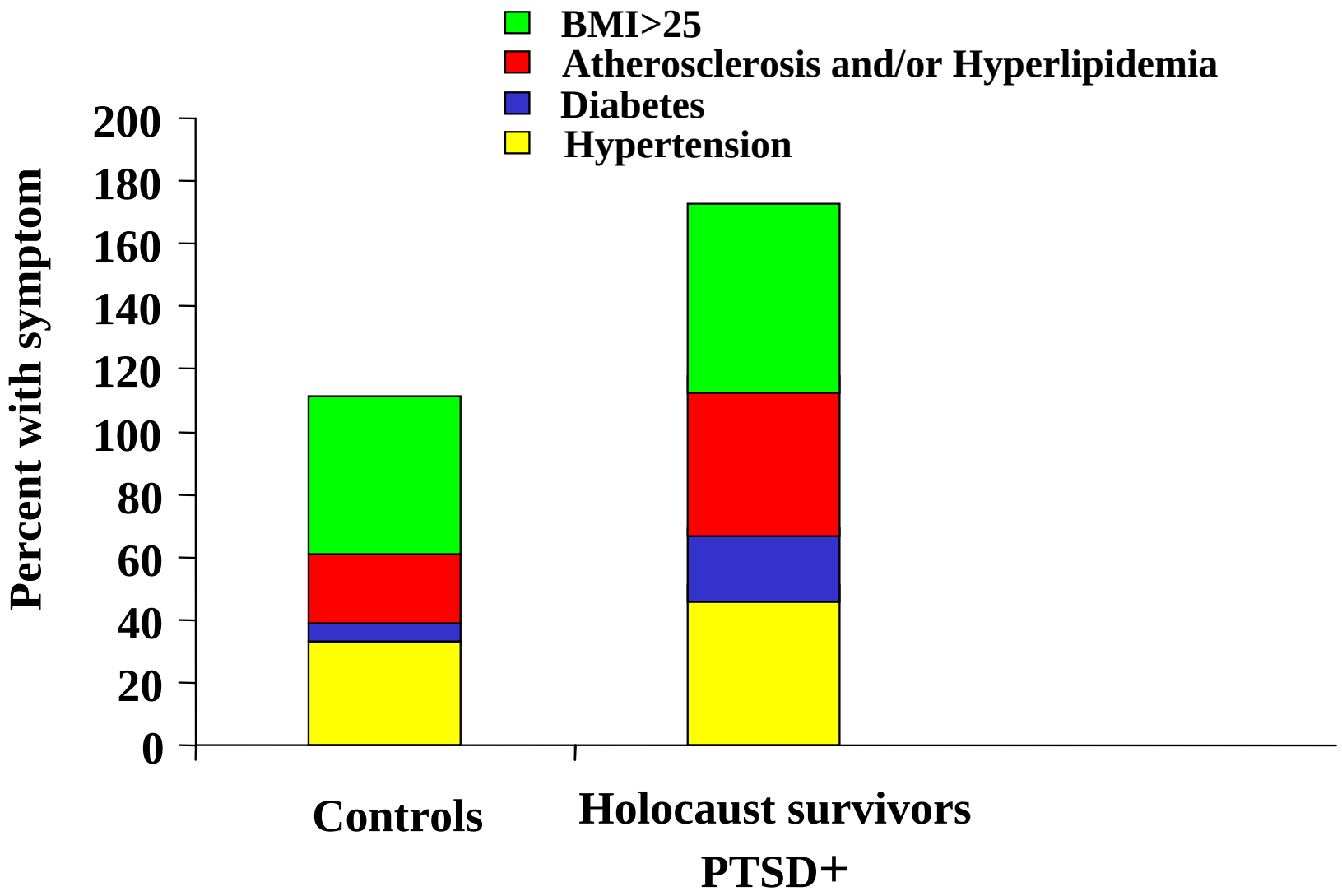




Source: Behavioral Risk Factor Surveillance System, CDC.

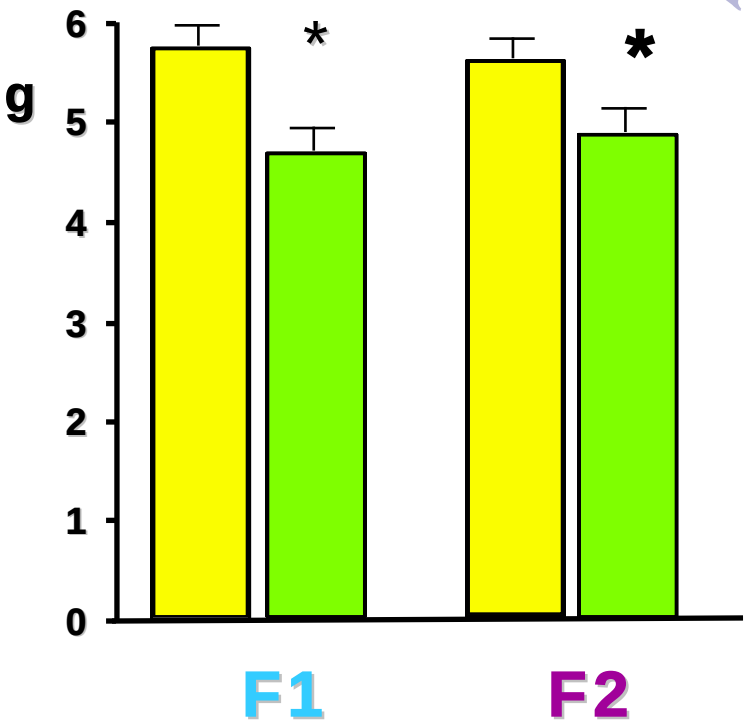
PTSD after Holocaust traumatisation associates with 'metabolic syndrome'



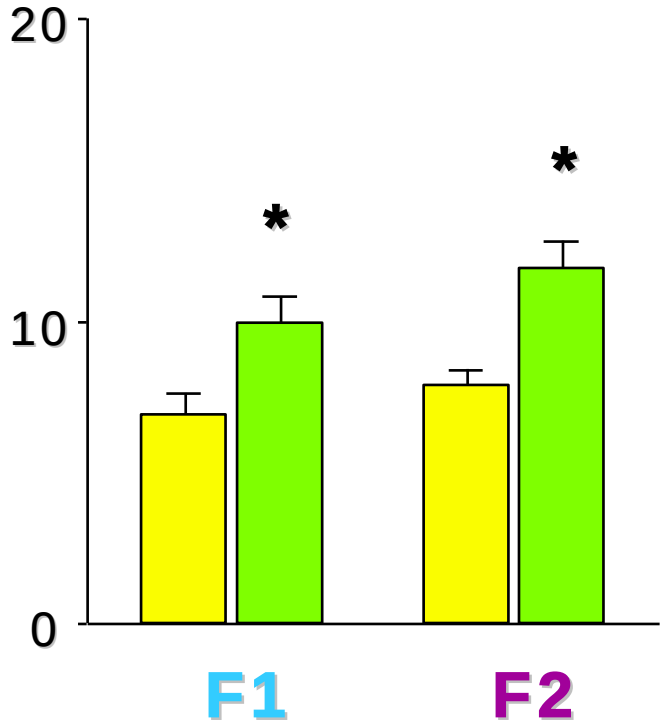
‘Intergenerational’ effects

Intergenerational effects of prenatal stress

Birth weight



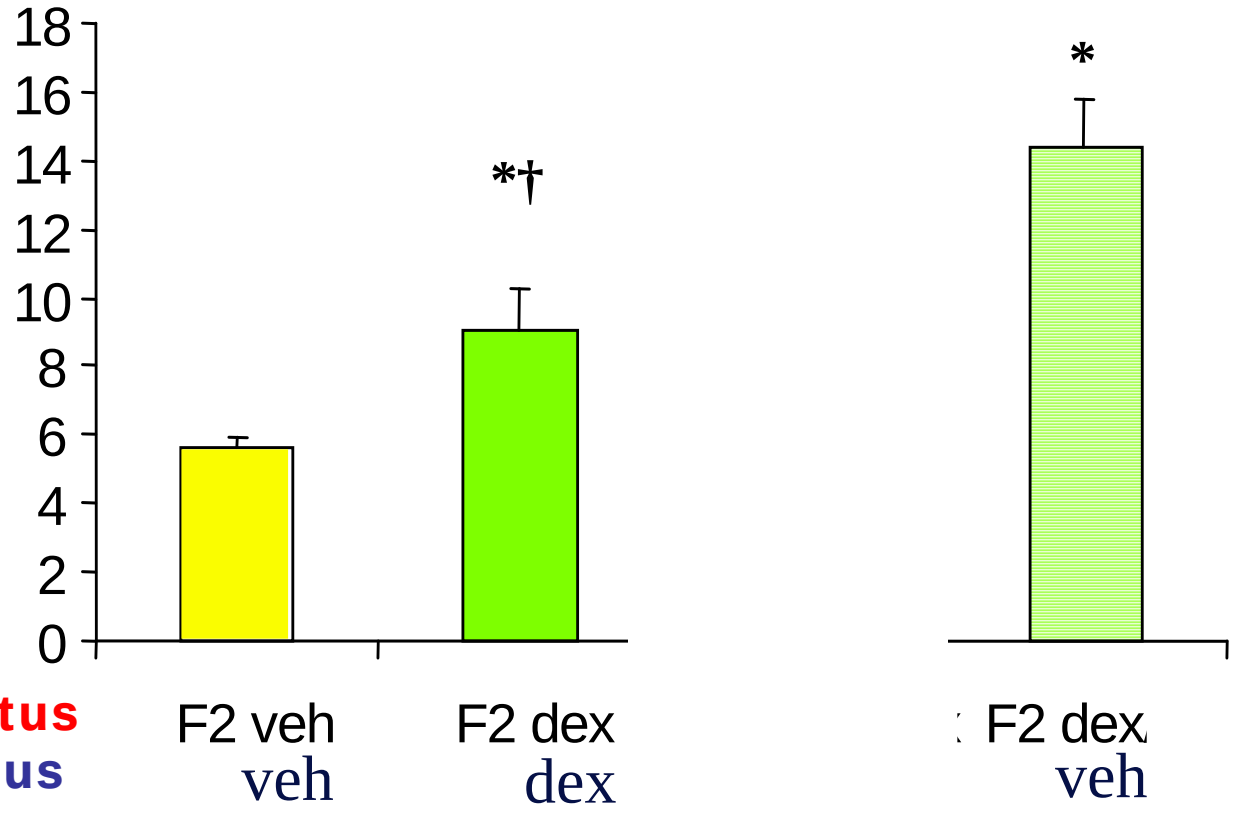
Glucose homeostasis



Drake et al, Am J Physiol 2005

Epigenetics?

Liver glucose production

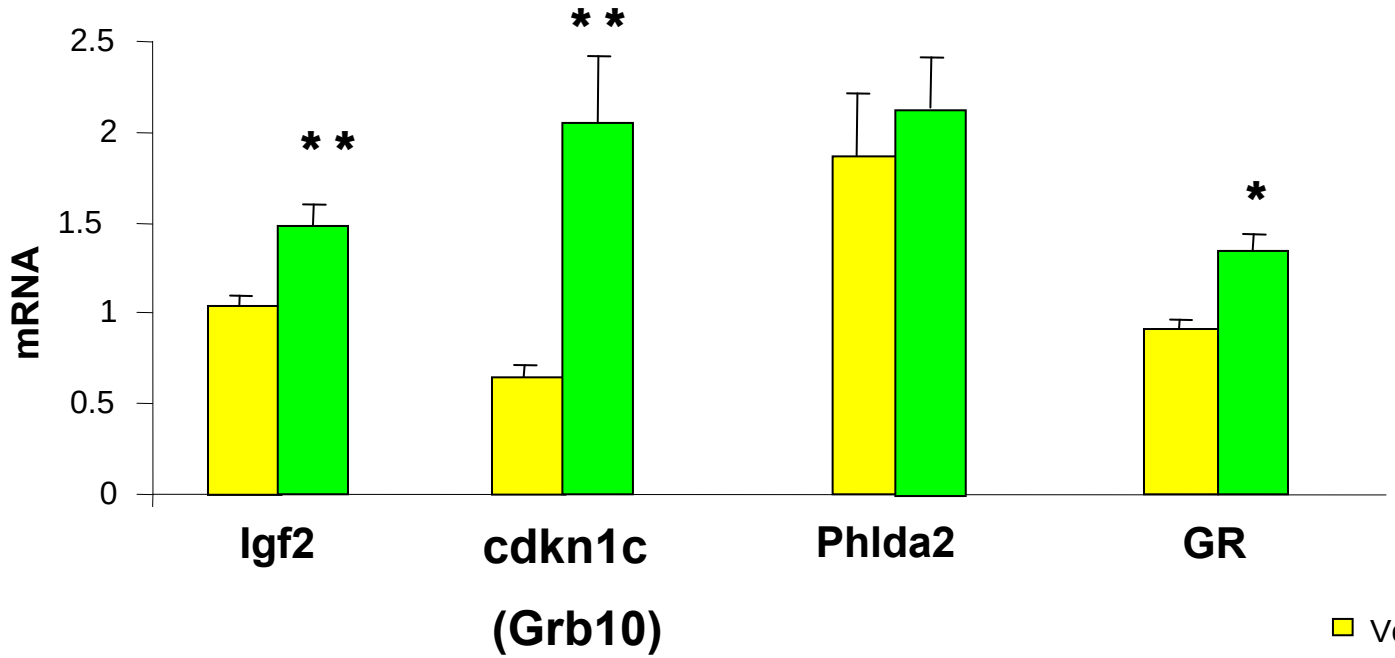


Mother as fetus
Father as fetus

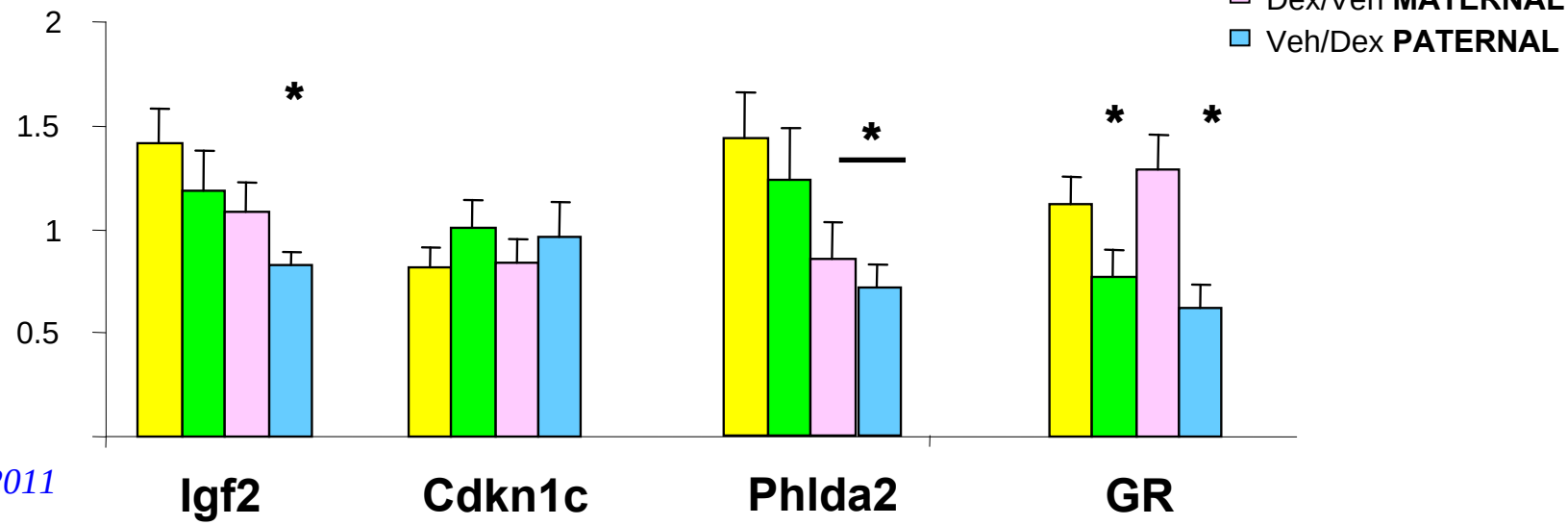
Drake et al, Am J Physiol 2005

The changes differ in the first and second generations

Fetal liver F1

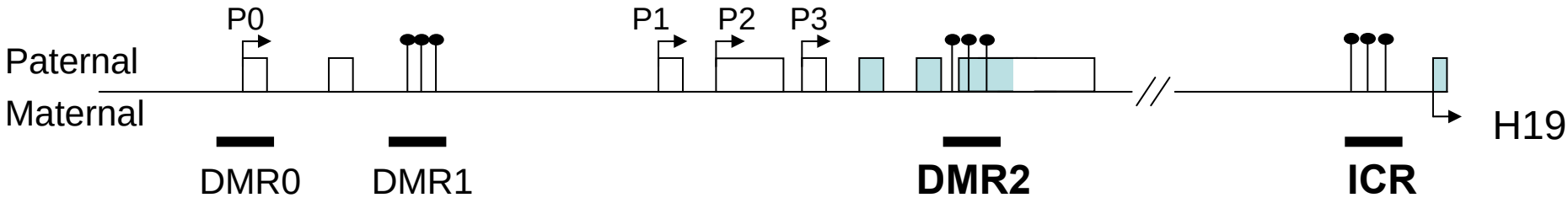


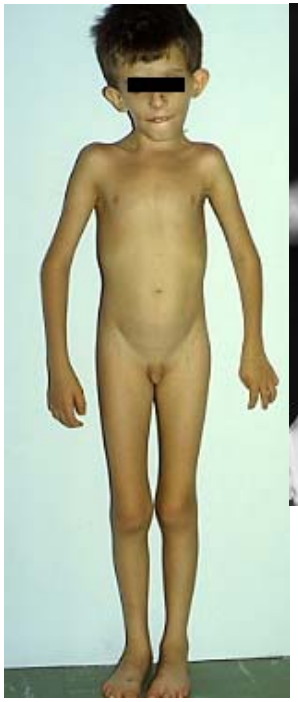
F2

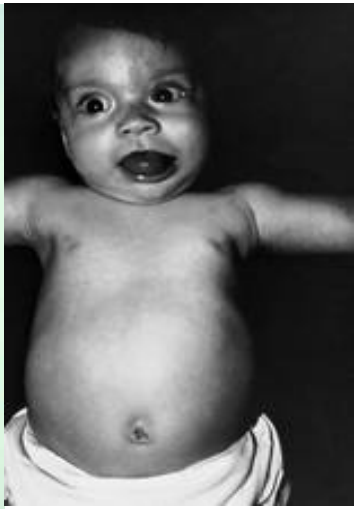


Drake et al, Epigenetics, 2011

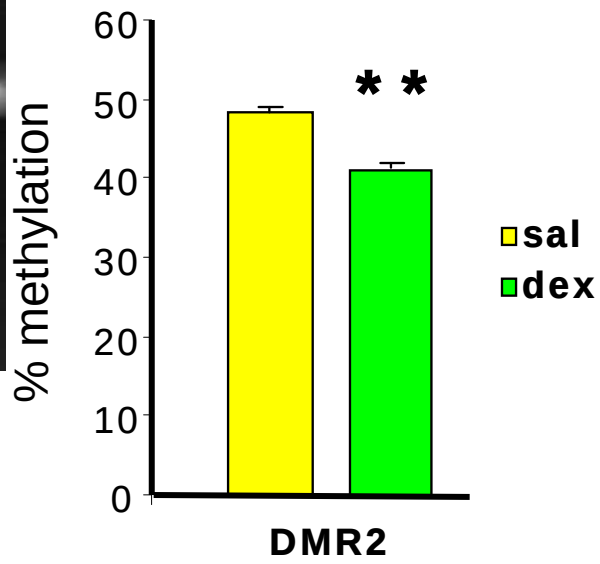
Epigenetic effects also differ in the first and second generations



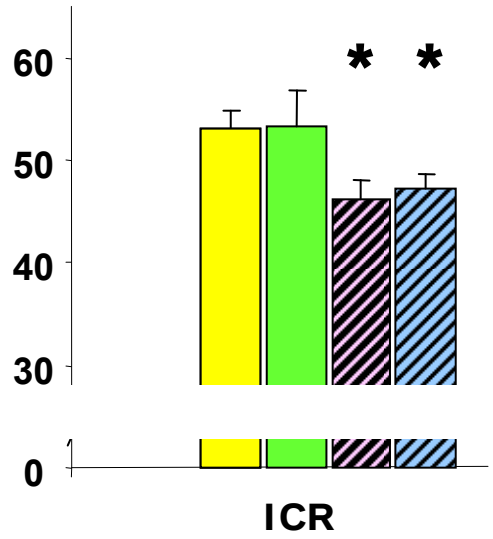




F1 = DMR2



F2 = ICR

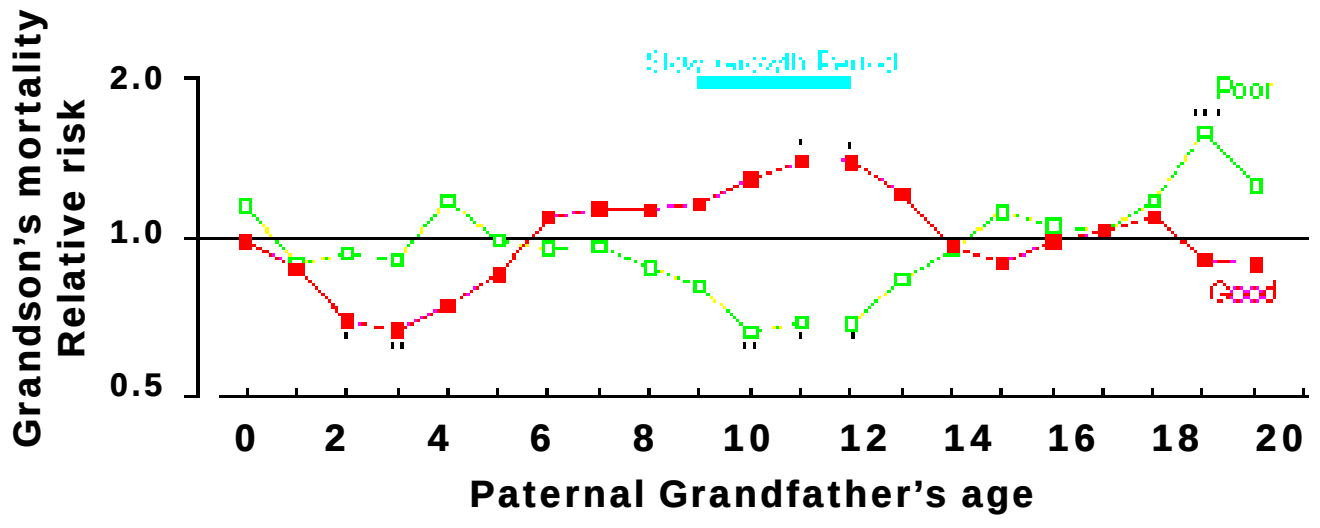


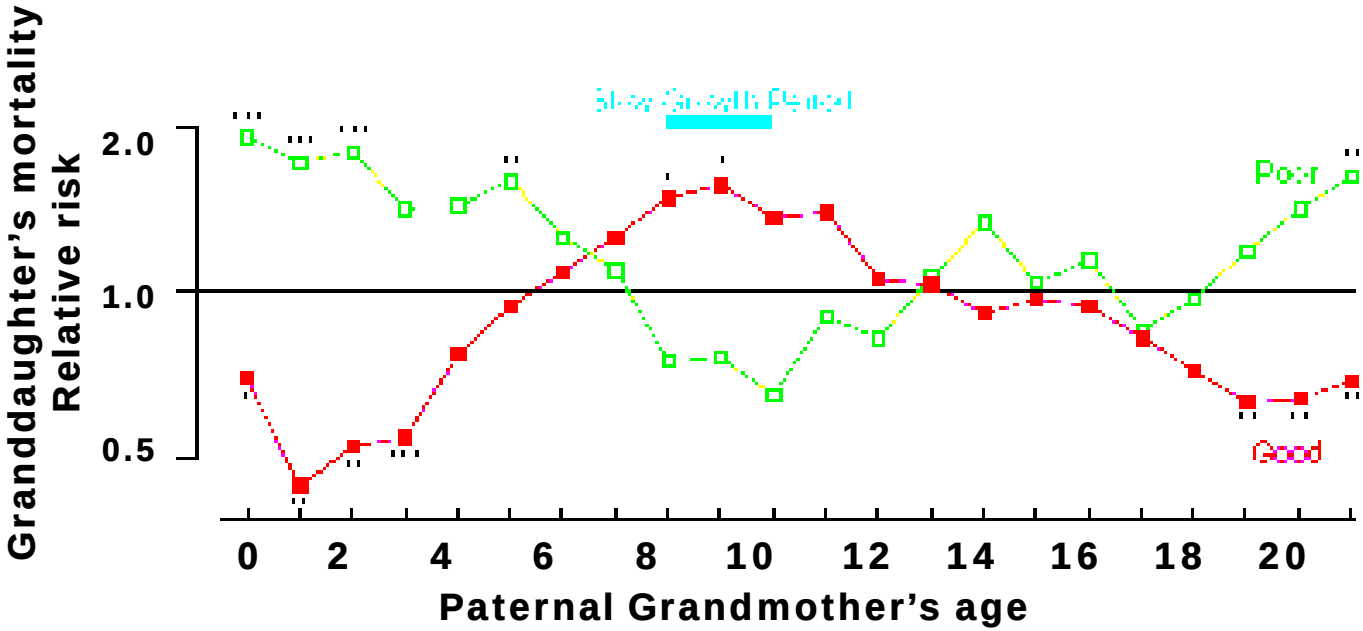
15-30% methylation difference in Beckwith-Weidermann and Silver-Russell syndromes

Drake et al, Epigenetics 2011

Overkalix

You are what your grandparents ate?





Grandparent's Nutrition in childhood

Poor

Good

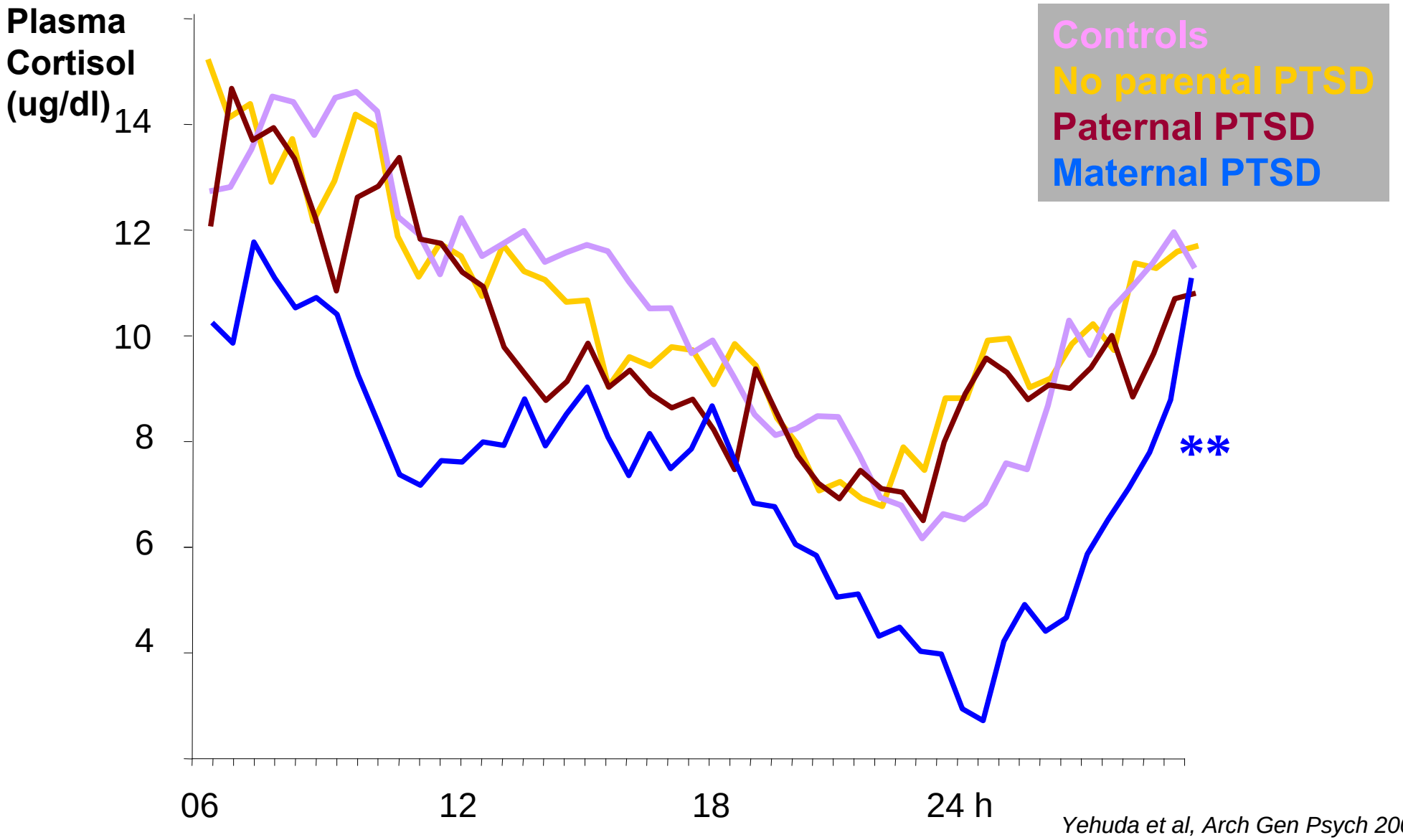
Pembrey et al, *Eur J Hum Gen, 2006*

And unto the next generation?

- 50% Holocaust survivors have PTSD (5-10% normal population)
- 30% of survivors' children have PTSD
- These children do not appear to have experienced more major trauma
- Holocaust exposure predicts offspring depression, ..but survivor PTSD predicts offspring PTSD

This suggests that parental PTSD is a 'vulnerability factor' for offspring PTSD

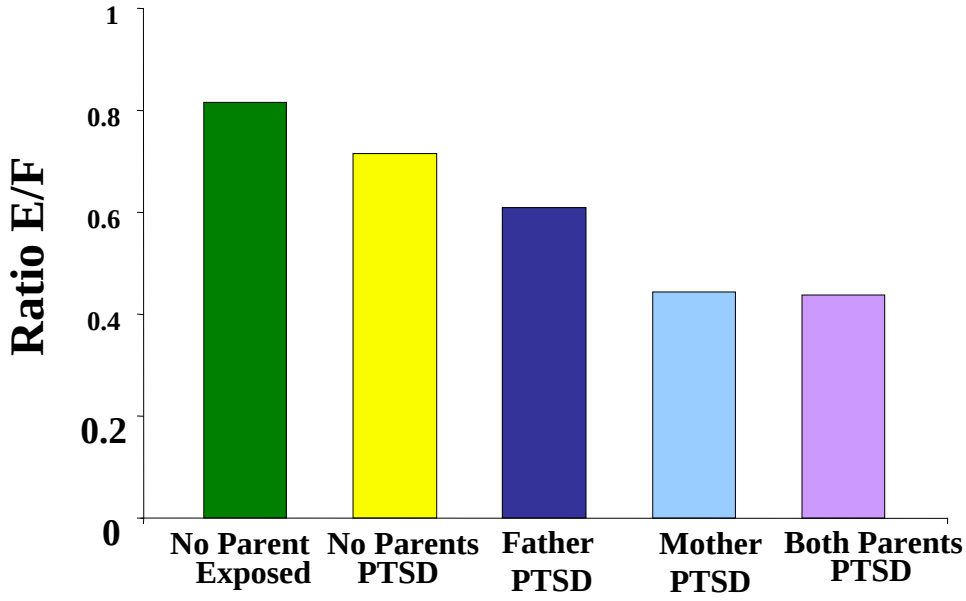
You are shaped by your mother's stress: maternal PTSD & her healthy offspring's cortisol



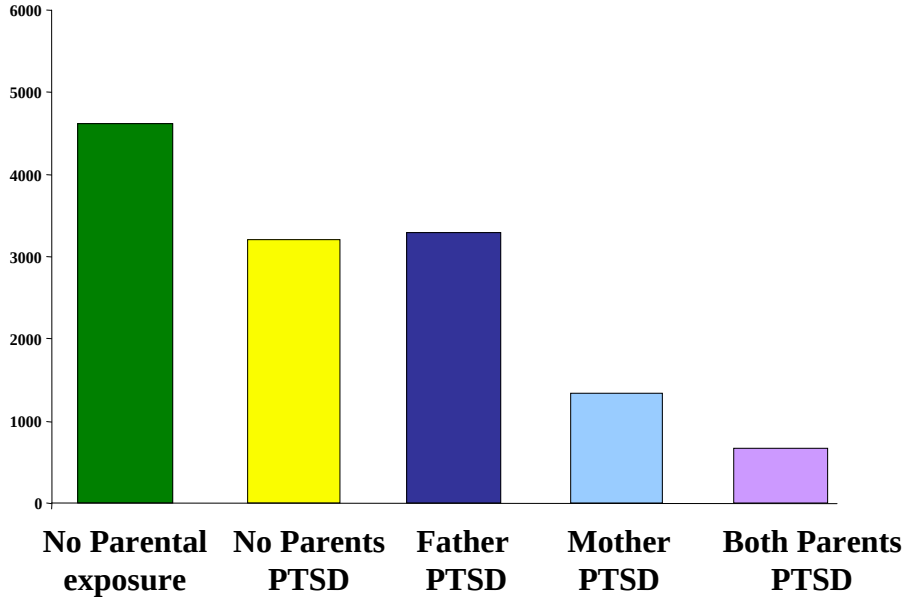
Yehuda et al, Arch Gen Psych 2008

Maternal PTSD also impacts steroid enzymes in her children

11β-HSD2



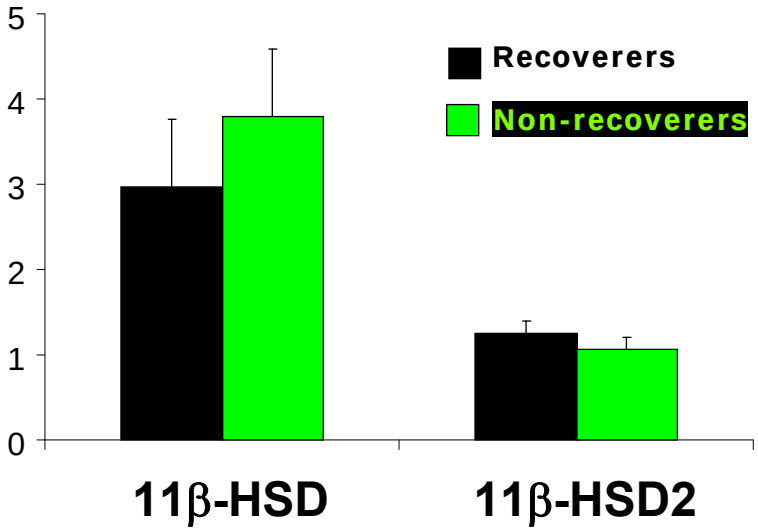
5α-reductase



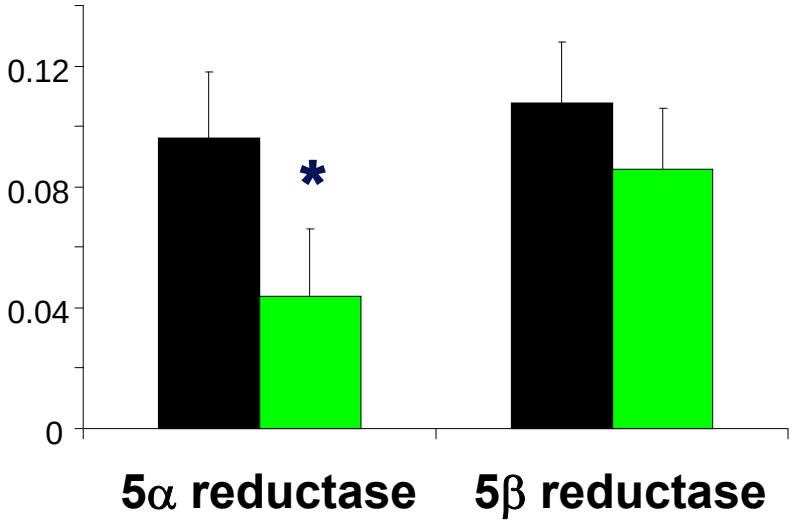
Yehuda et al, unpublished

9.11 study
lower 5α-reductase predicts PTSD

11β-HSDs



A ring reductases



Yehuda et al, *Psychoneuroendocrinology 2009*

So what can be done?

The 1960s Motherwell diet

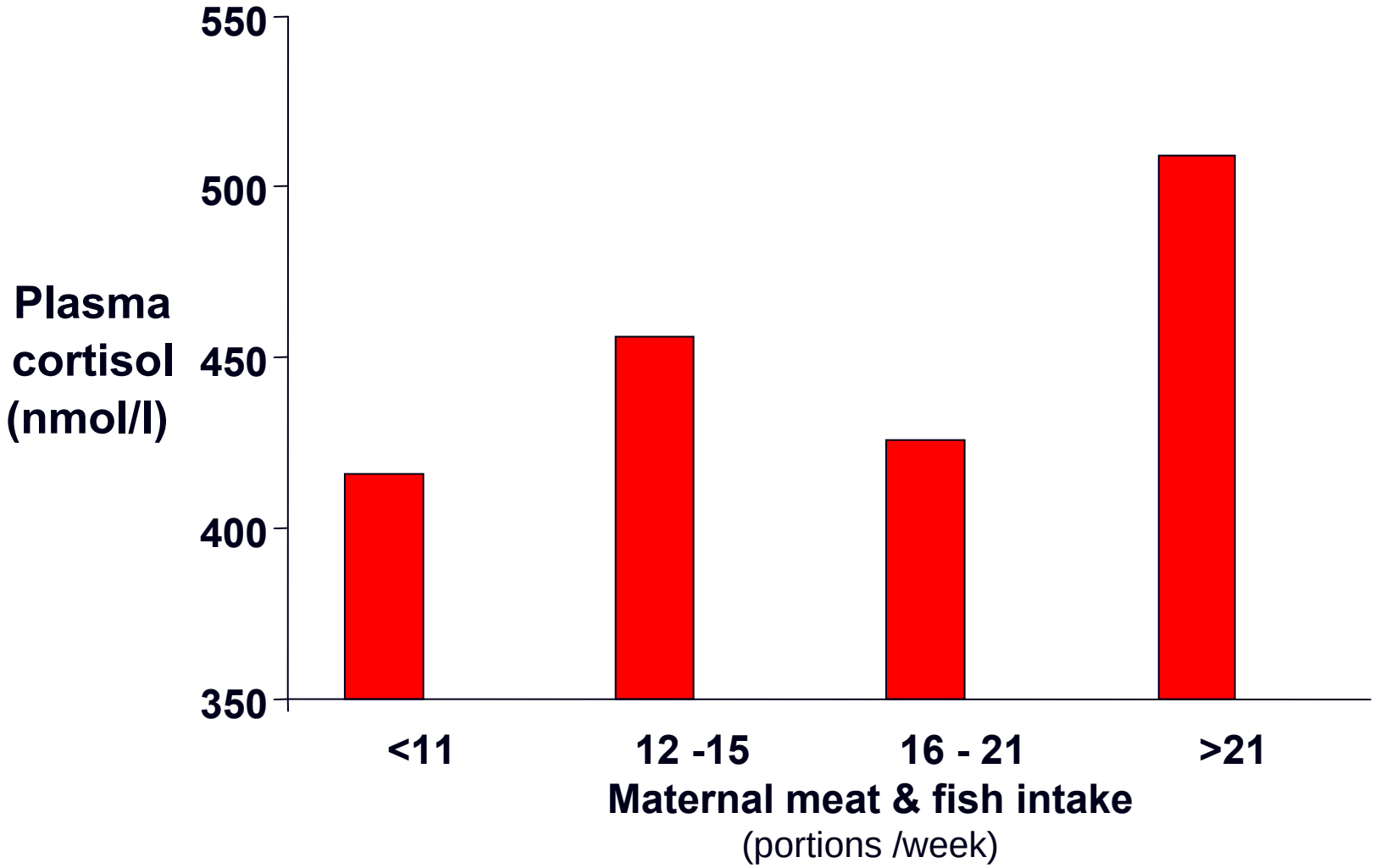
IMPORTANT. This is a special diet for expectant mothers. If you ADD to it or TAKE from it, it is no longer special

1. Meat – **One pound of red meat should be eaten every day of gestation. Quantity is more important than quality.**
2. Green vegetables – try to eat twice daily. Do not eat peas, beans, turnip, parsnip, carrot or beetroot
3. Sweets – should be limited to ½ pound of boiled sweets per week. Do not eat chocolate
4. Do not eat potatoes or chips, breads, rolls, scones, cakes or biscuits of any kind
5. Do not eat milk puddings, cereals, macaroni, spaghetti and ice cream

If you persevere with this diet for three weeks it becomes natural and easy……

The advantages of success in controlling your diet……come only if you are successful, not just trying

HF in pregnancy: increased cortisol in 30y offspring

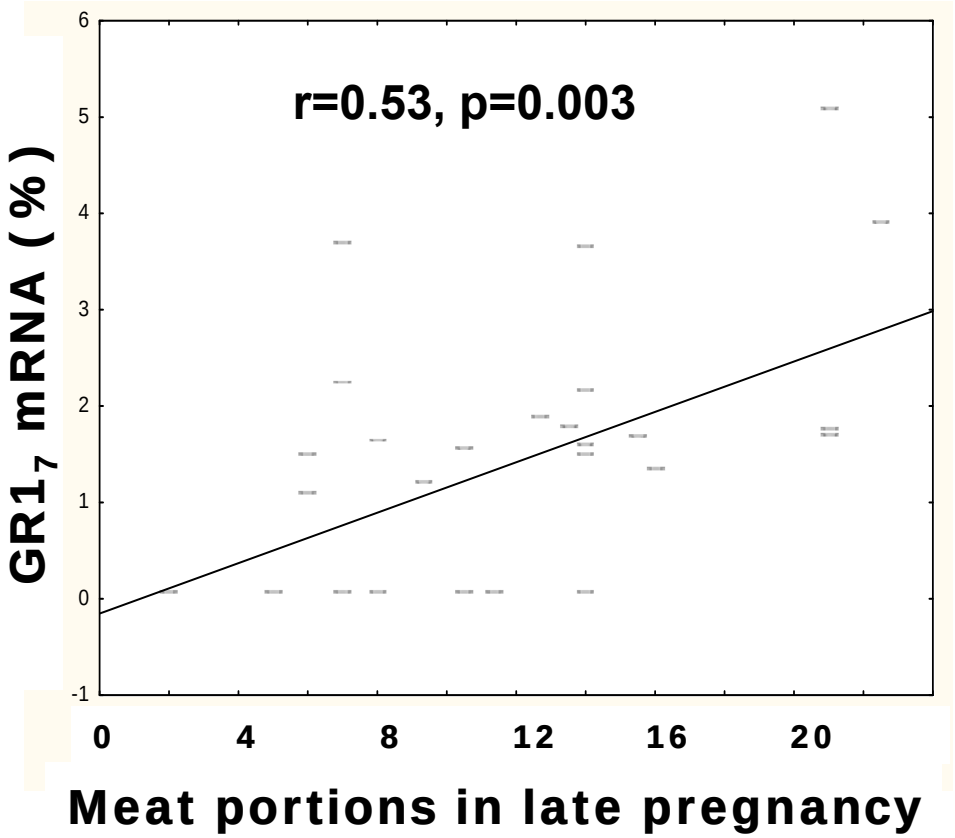


trend p<0.05

Reynolds et al, JCEM 2007

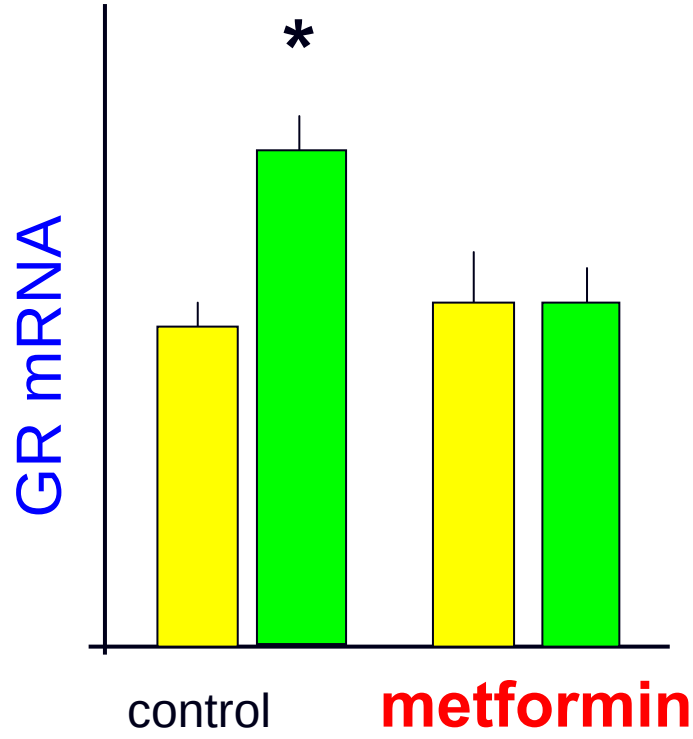
Biomarkers and stratified therapy?

Adult GR 1_7 and maternal diet



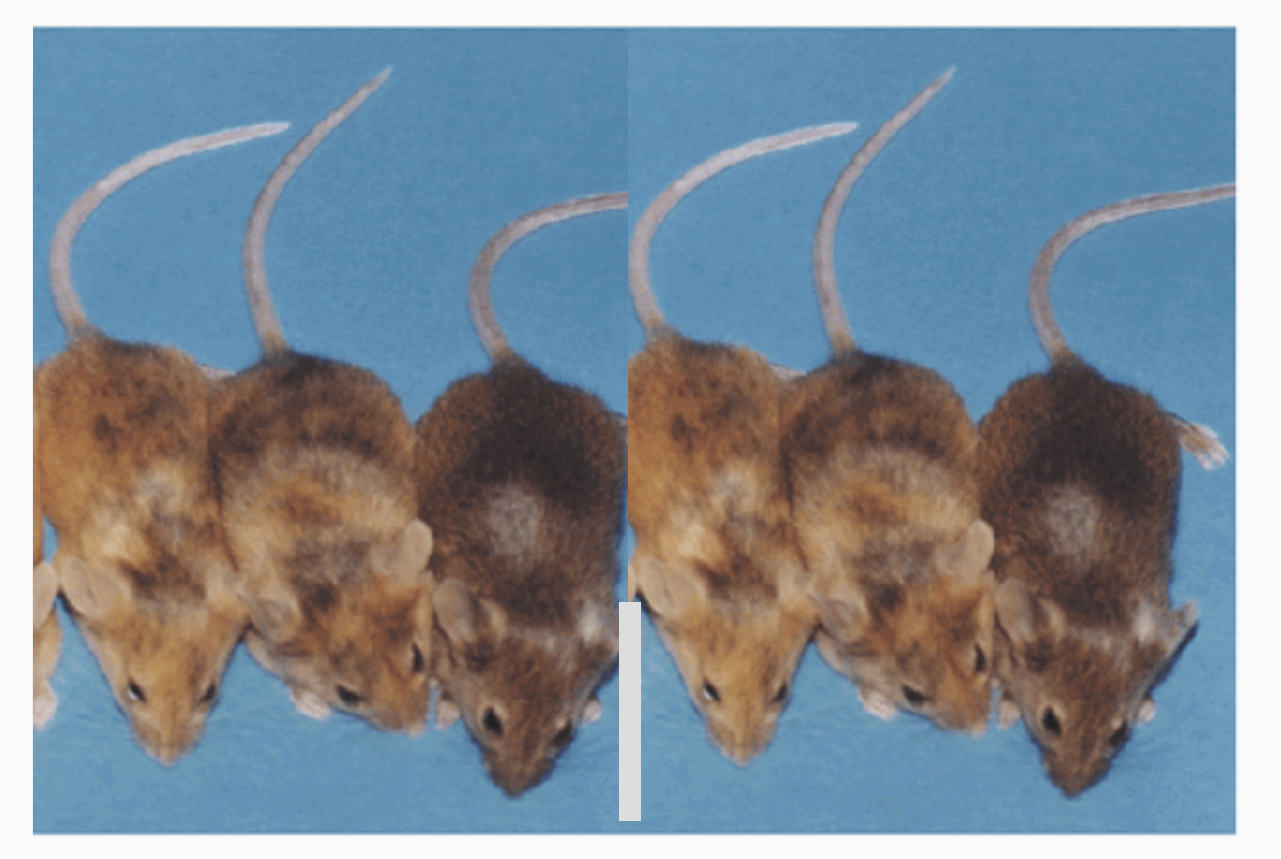
Reynolds, Drake et al, unpublished

Metformin reverses increased liver GR



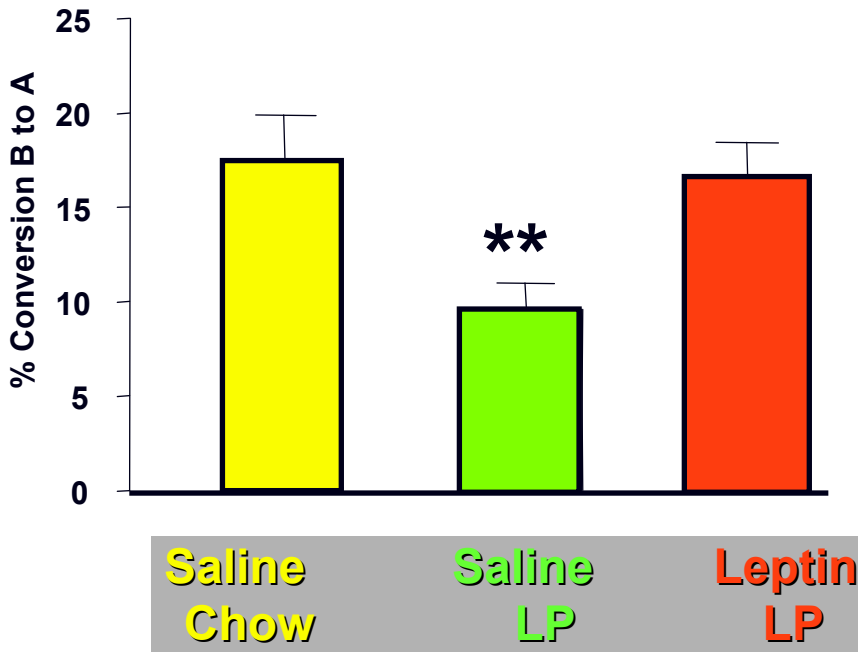
Cleasby et al, Endo, 2003

Give methyl donors (folate, choline, Vit B12, betaine)

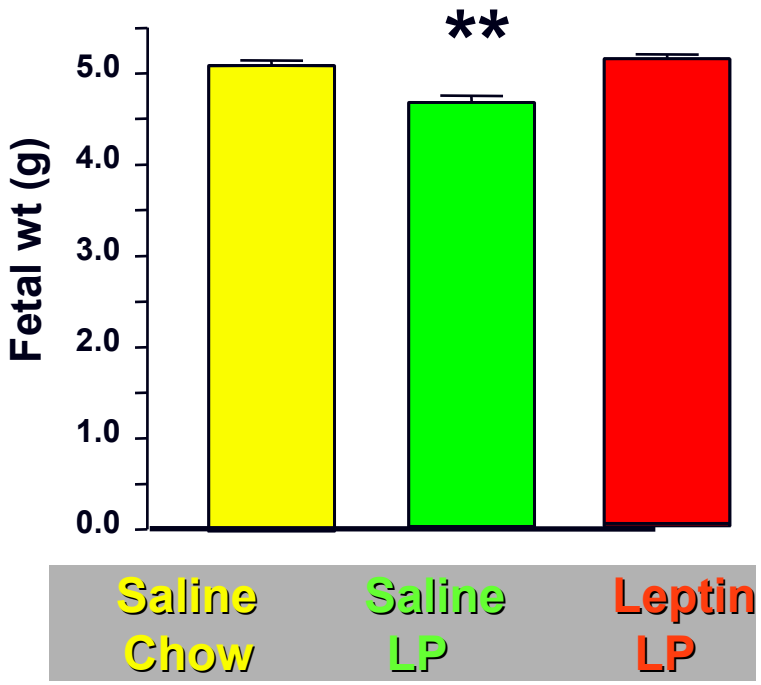


Leptin reverses low protein effects on placental 11β-HSD2 and birth wt

Placental 11β-HSD2 activity



Fetal wt



Stocker et al, Int J Ob, 2004

Summary

- A variety of environmental factors ‘programme’ the offspring for the lifespan
- The outcomes of different maternal challenges are rather similar
- Maternal stress and its glucocorticoid hormone mediators is a powerful programming influence
- Placental 11β-HSD2 affords one link between maternal, placental and fetal environments
- Epigenetic alterations are likely to underpin some of these effects
- The brain is particularly vulnerable to fetal programming
- Programmed changes in glucocorticoid metabolism may impact vulnerability to mood disorders, notably PTSD
- Effects persist into a second generation
- Not everything is written in your genes and epigenes

And the Future?

- We don’t yet know how important these early life impacts are, nevertheless..
- Epigenetic marks may measure individual exposure and risk
- They are relatively stable, unlike many blood tests and other measures in adult life
- Epigenetic changes are also potentially modifiable, unlike genetics
- If we can understand the ‘rules’ we may be able to target screening and ‘prevention’ to those at greatest risk
- We may also find ways to personalise therapy depending on the individual ‘cause’ of disease
- However, this biology has survived hundreds of millions of years of evolution because, on balance, it is beneficial to the individual, so interfering blindly may give unwanted consequences

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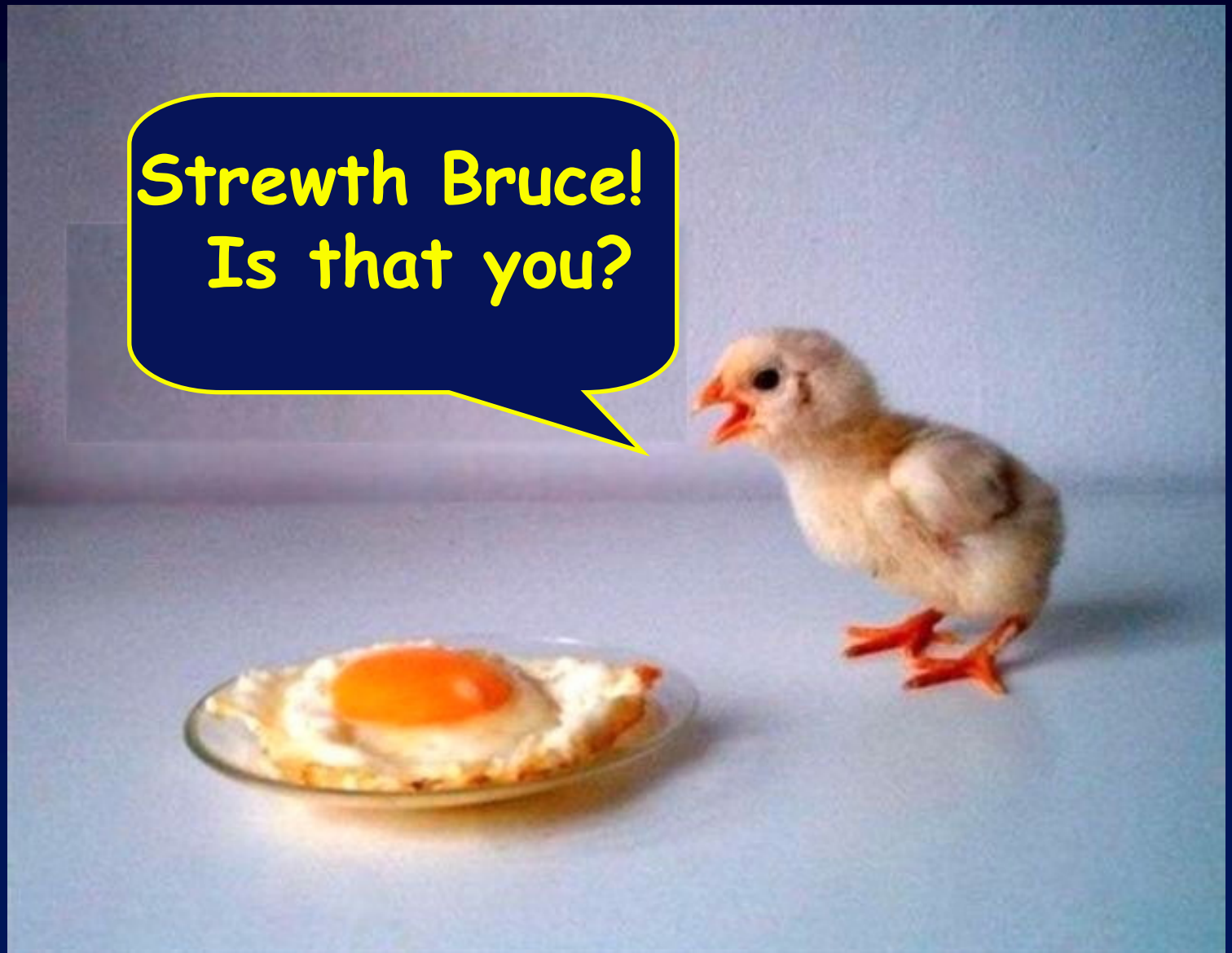
We can’t avoid early life stress



Methyl donor (icv) methylates $GR1_7$ in adult hippocampus