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
"Without stress, there would be no life"

Hans Selye
Glucocorticoids

- 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
Cushing's Disease

- High blood pressure
- Diabetes
- High blood cholesterol
- Abdominal obesity
- Stretch marks
- Bruising
- Osteoporosis
- Muscle weakness
- Infertility
- Depression
- Memory loss
Nature and nurture
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)

<table>
<thead>
<tr>
<th>Weight at Birth</th>
<th>Weight 1st Year</th>
<th>Food</th>
<th>No. of Visits</th>
<th>Condition, and Remarks of Health Visitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 1/2 lbs</td>
<td>24 1/2 lbs</td>
<td>13</td>
<td>11</td>
<td>y</td>
</tr>
<tr>
<td>Healthy &amp; well developed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 lbs</td>
<td>18 1/2 lbs</td>
<td>13</td>
<td>12</td>
<td>h. y. y. y.</td>
</tr>
<tr>
<td>Moved to Bury Green St. Hadham.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 1/2 lbs</td>
<td>22 lbs</td>
<td>9</td>
<td>9</td>
<td>y. y. y. y.</td>
</tr>
<tr>
<td>Healthy &amp; normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: The table contains historical data about the weight and health of a child, including visits from a health visitor.*
Birth weight and adult disease

Barker et al, 1990, BMJ, 301:259
Low birth weight and risk of T2D/MS

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

Birth weight and depression aged 68 years

Odds ratio

<table>
<thead>
<tr>
<th>Category</th>
<th>Odds Ratio</th>
</tr>
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<tbody>
<tr>
<td>&lt;6.5</td>
<td>3.0</td>
</tr>
<tr>
<td>6.5-7.5</td>
<td>2.5</td>
</tr>
<tr>
<td>7.5-8.5</td>
<td>2.0</td>
</tr>
<tr>
<td>&gt;8.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

P = 0.02

from the Hertfordshire cohort study: Thompson et al BJPsych 2001
Plasma cortisol in 64y old men correlates negatively with birth weight

Birth weight and adult disease

low birth weight

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

- Increased overall mortality

8.7 lbs  5.3 lbs
4 kg     2.4 kg
Butterflies hatched during different seasons were coloured differently. Season-dependent colouration mimicked by larval incubation temperature.

Weissman 1893
• 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

Possible mechanisms

• genetics

8.7 lbs (4 kg)  5.3 lbs (2.4 kg)
Mechanisms linking to adult disease

Possible mechanisms
- genetics
- Socio-economic class

8.7 lbs (4 kg)  5.3 lbs (2.4 kg)
Mechanisms linking to adult disease

Possible mechanisms

- genetics
- socio-economic class
- maternal malnutrition

8.7 lbs (4 kg)  5.3 lbs (2.4 kg)
Pre-natal starvation...
Dutch Hunger Winter 1945 and Chinese Famine 1959-61

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

'We Were So Hungry We Ate Tulips'
Father Leo Zonneveld
Mechanisms linking to adult disease

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.

**Systolic BP**

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
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<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
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</table>

**Insulin (ins)** and **Glucose (glu)**

<table>
<thead>
<tr>
<th></th>
<th>Ins</th>
<th>Glu</th>
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<tbody>
<tr>
<td>No inject</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dex wk 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dex wk 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dex wk 3</td>
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</table>

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


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 11β-hydroxysteroid dehydrogenase protects the foetus from maternal glucocorticoids
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 hypertension. 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 (11β-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.

Deficiency of the placental cortisol barrier and reduced birth weight

**rnat**

**human**

Placental 11β-HSD2 activity
Placental 11β-HSD2 predicts BP at 3yrs

362 US babies

Huh et al, BMC Med 2008
**11ß-HSD inhibition programmes increased blood pressure and glucose**

Lindsay et al, *Hypertension*, 1996
Lindsay et al, *Diabetologia*, 1996
Placental $11\beta$-HSD2 deficiency: key to developmental programming?

Protein restriction

<table>
<thead>
<tr>
<th>Protein restriction</th>
<th>stress</th>
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<tr>
<td>22%</td>
<td>35%</td>
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<tr>
<td>18%</td>
<td>30%</td>
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<tr>
<td>9%</td>
<td>25%</td>
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</tbody>
</table>

Placental GC barrier

- diet
- stress
- disease

• 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**

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

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

Nyirenda et al, JCI, 1998; Cleasby et al, Endo, 2003; Levitt et al, Neuroendocrinol, 1996
The GR gene contains multiple alternate, tissue-specific 1st exons

<table>
<thead>
<tr>
<th>1st exons</th>
<th>Liver</th>
<th>Hippoc</th>
<th>Thymus</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>17</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
</tbody>
</table>

McCormick et al, Mol Endo, 2000
5HT regulates hippocampal GR gene transcription

5HT → PKA → cAMP → Ca++ → AP2, NGFI-A → GR gene

5HT regulates hippocampal GR gene transcription through the 5HT receptor pathway, which involves PKA, cAMP, and Ca++. This pathway leads to the activation of AP2 and NGFI-A, which in turn upregulate the GR gene transcription.
How can early life events affect someone for the rest of their lifespan?

epigenetics
sub-group *Cassiope*, lately brought from Bow island, in the Low Archipelago. Of Cassiope, 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 hawk 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 these 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 Cassiope is somewhat like that of a starling; and that of the fourth sub-group, *Camarhynchus*, is slightly pear-shaped. Seeing this gradation and diversity of structure in one small, intimately related group of birds, one might really fancy that from an original pugnacity of birds in this archipelago, one species had been taken and modified for different ends. In a like manner it might
(a) Diagram showing an inverted repeat, hair-cycle-specific non-coding exons, and coding exons.

(b) Image of mice with varying fur colors.
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\textsubscript{7} promoter.

**NGFI-A**

\[ \text{CpG} \]

Weaver et al, Nature Neurosci 2004
Lower total DNA methylation with low SES

The excitement of steroid metabolism
Children exposed to the Holocaust
## Lower glucocorticoid metabolism in Holocaust survivors

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=22)</th>
<th>Holocaust survivors (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total glucocorticoids</strong></td>
<td>11000 ± 1200</td>
<td>6500 ± 600*</td>
</tr>
<tr>
<td><strong>5α-THF</strong></td>
<td>5600 ± 600</td>
<td>2500 ± 400**</td>
</tr>
<tr>
<td><strong>5β-THF</strong></td>
<td>1900 ± 400</td>
<td>1600 ± 300</td>
</tr>
<tr>
<td><strong>5α-red ratio</strong></td>
<td>17 ± 4</td>
<td>5.6 ± 0.7**</td>
</tr>
<tr>
<td><strong>5β-red ratio</strong></td>
<td>8.0 ± 1.5</td>
<td>7.4 ± 1.4</td>
</tr>
<tr>
<td><strong>11β-HSD2 ratio</strong></td>
<td>1.23 ± 0.08</td>
<td>0.99 ± 0.08**</td>
</tr>
</tbody>
</table>

Yehuda et al, J Psychiatr Res 2009
Younger at trauma - greater decrease in metabolism

Steroid metabolism

Age at trauma ‘exposure’

0 5 10 15 20 years

‘normal’ range
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

$11\beta\text{-HSD2}$

cortisol $\underset{5\alpha\text{-reductase}}{\longrightarrow}$ cortisone

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)
Obesity Trends* Among U.S. Adults
**BRFSS, 1990**

(*BMI ≥30, or ~30 lbs overweight for 5’4” woman*)
Obesity Trends* Among U.S. Adults

BRFSS, 1995

(*BMI ≥30, or ~ 30 lbs overweight for 5’4” woman)
Obesity Trends* Among U.S. Adults
BRFSS, 2000
(*BMI ≥30, or ~ 30 lbs overweight for 5’4” woman)
Obesity Trends* Among U.S. Adults
BRFSS, 2005

(*BMI ≥30, or ~ 30 lbs overweight for 5’4” woman)
Obesity Trends* Among U.S. Adults
BRFSS, 2010
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

Source: Behavioral Risk Factor Surveillance System, CDC.
PTSD after Holocaust traumatisation associates with ‘metabolic syndrome’

- BMI > 25
- Atherosclerosis and/or Hyperlipidemia
- Diabetes
- Hypertension
‘Intergenerational’ effects
Intergenerational effects of prenatal stress

Birth weight

Glucose homeostasis

Drake et al, Am J Physiol 2005
Liver glucose production

Drake et al, Am J Physiol 2005
The changes differ in the first and second generations.

**Fetal liver F1**

The changes differ in the first and second generations.

**F2**

Drake et al, Epigenetics, 2011
Epigenetic effects also differ in the first and second generations

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

Drake et al, Epigenetics 2011
Overkalix
You are what your grandparents ate?

Pembrey et al, Eur J Hum Gen, 2006

Grandparent’s Nutrition in childhood

Poor

Good
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

Plasma Cortisol (ug/dl)

Controls
No parental PTSD
Paternal PTSD
Maternal PTSD

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 $5\alpha$-reductase predicts PTSD

11$\beta$-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 $\frac{1}{2}$ 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

Plasma cortisol (nmol/l)

- <11
- 12 - 15
- 16 - 21
- >21

Maternal meat & fish intake (portions/week)

Trend p<0.05

Reynolds et al, JCEM 2007
Biomarkers and stratified therapy?

**Adult GR 17 and maternal diet**

![Graph showing the relationship between meat portions in late pregnancy and GR17 mRNA (%).](image1)

- $r=0.53$, $p=0.003$

**Metformin reverses increased liver GR**

![Graph showing the effect of metformin on GR mRNA levels.](image2)

- *Cleasby et al, Endo, 2003*

*Reynolds, Drake et al, unpublished*
Give methyl donors (folate, choline, Vit B12, betaine)
Leptin reverses low protein effects on placental 11β-HSD2 and birth 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
<table>
<thead>
<tr>
<th>Edinburgh</th>
<th>Collaborations</th>
<th>Collaborations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amanda Drake</td>
<td>Mt Sinai, New York</td>
<td>Helsinki</td>
</tr>
<tr>
<td>Lizzy Cottrell</td>
<td>Rachael Yehuda</td>
<td>Katri Raikkonen</td>
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<tr>
<td>Caitlin Wyrewoll</td>
<td>Linda Bierer</td>
<td>Johan Eriksson</td>
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<tr>
<td>Rafn Benediktsson</td>
<td>South Hampton</td>
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<tr>
<td>Robbie Lindsay</td>
<td>David Barker</td>
<td>Dallas</td>
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<tr>
<td>Roger Brown</td>
<td>David Phillips</td>
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<tr>
<td>Moffat Nyirenda</td>
<td>Keith Godfrey</td>
<td>David Russell</td>
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<td>Mark Cleasby</td>
<td>Simon Langley-Evans</td>
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<td>Lincoln Liu</td>
<td>Mark Hanson</td>
<td>Mala Mahendroo</td>
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<td>Chris Kenyon</td>
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<tr>
<td>Dawn Livingstone</td>
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<td>Rebecca Reynolds</td>
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<td>Ruth Andrew</td>
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<td>Richard Meehan</td>
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<td>11β-HSD KOs</td>
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<td>John Mullins</td>
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<td>Janice Paterson</td>
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<td>Yuri Kotelevtsev</td>
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We can’t avoid early life stress

Strewth Bruce! Is that you?
Methyl donor (icv) methylates GR1 in adult hippocampus