

Neurodevelopmental implications of stress and endogenous glucocorticoid exposure during fetal development.



Vivette Glover
Imperial College London
January 2012

Environment Special:
The oceans—why 70%
of our planet is in danger

The Facebook Movie:
The secret history of
social networking

TIME



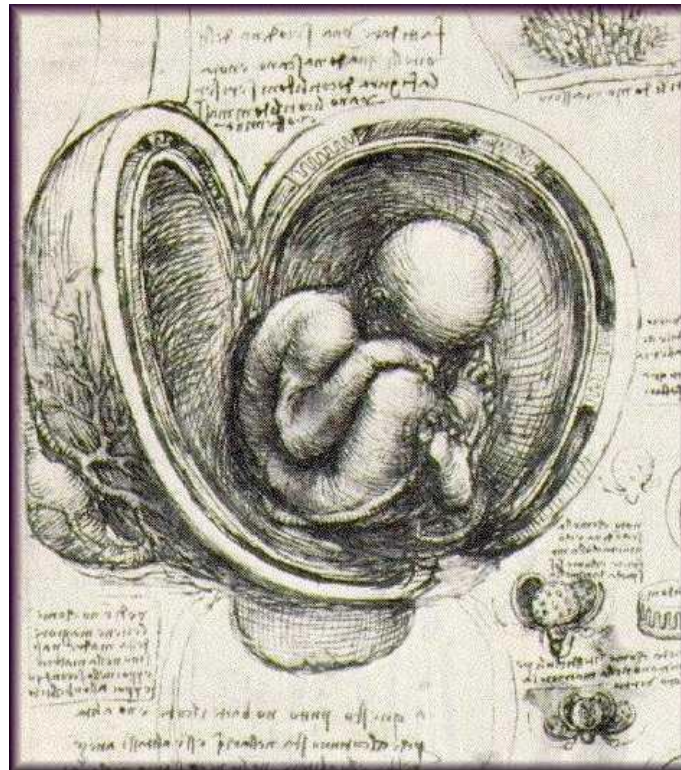
How the first nine months shape the rest of your life

The new science
of fetal origins

BY ANNIE MURPHY PAUL

The things desired by the mother are often found impressed on the child that the mother carries.

Leonardo Da Vinci



Fetal programming

Environment in utero ,
during different sensitive periods
for specific outcomes,
can alter the development
of the fetus,
with a permanent effect
on the child.



From fetus

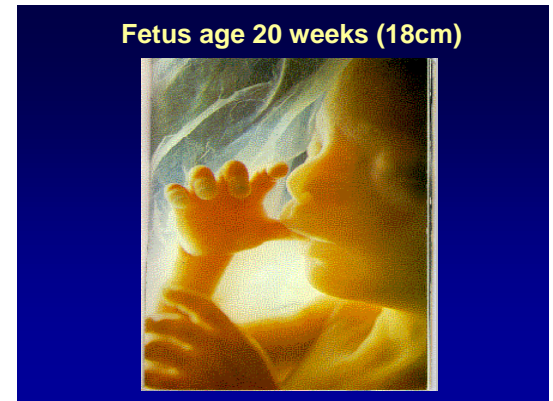


To child

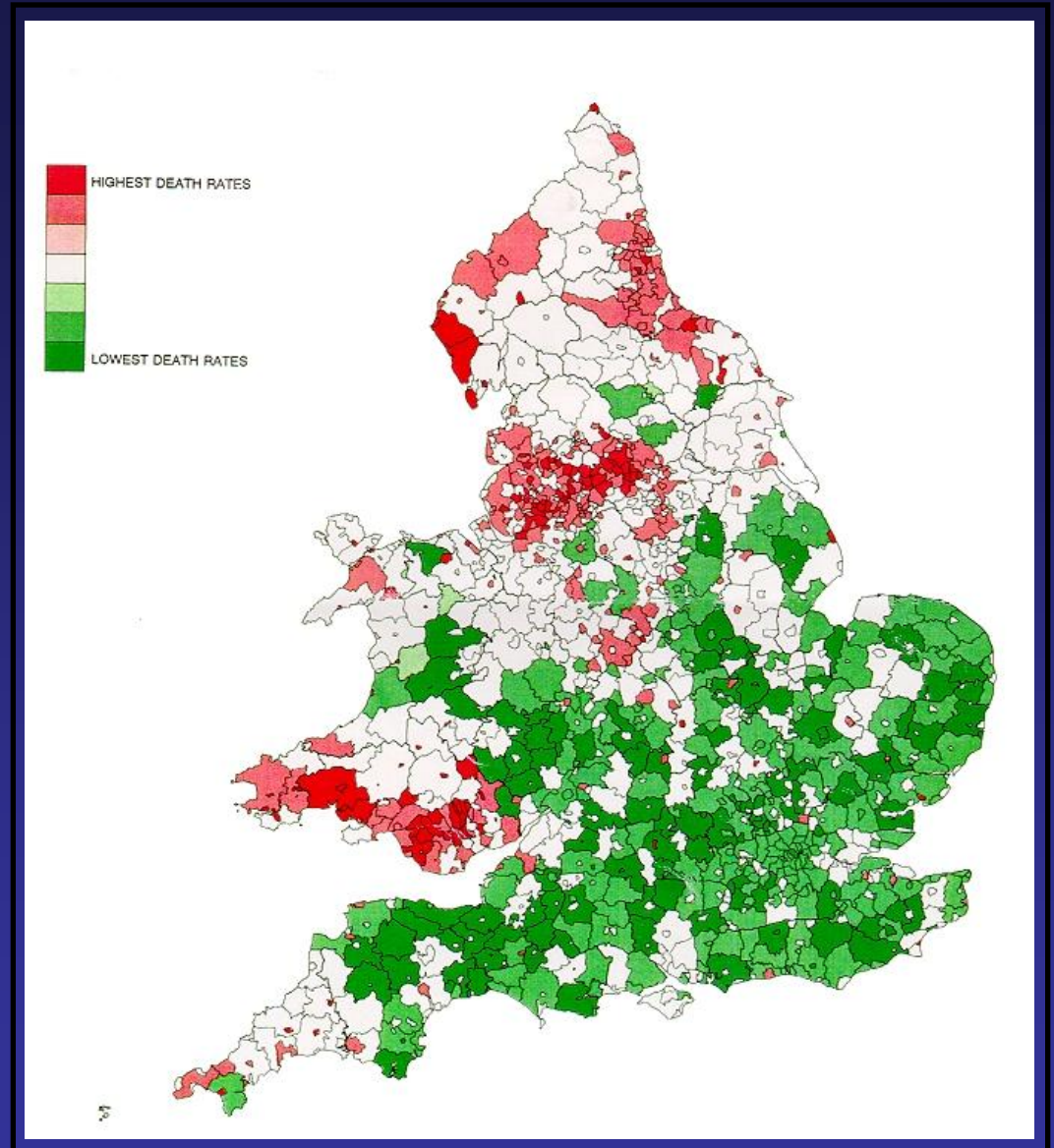
The fetal origins of adult disease hypothesis

David Barker

Coronary heart disease, Type 2 diabetes, stroke and hypertension originate in developmental plasticity, in response to undernutrition during fetal life

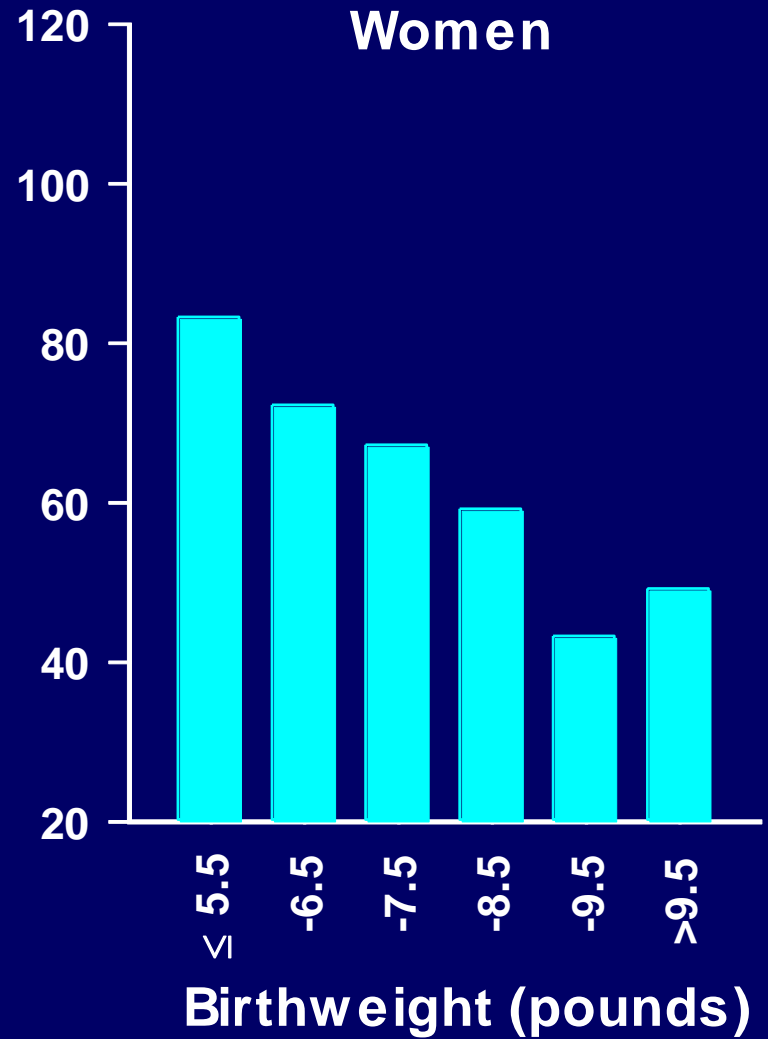
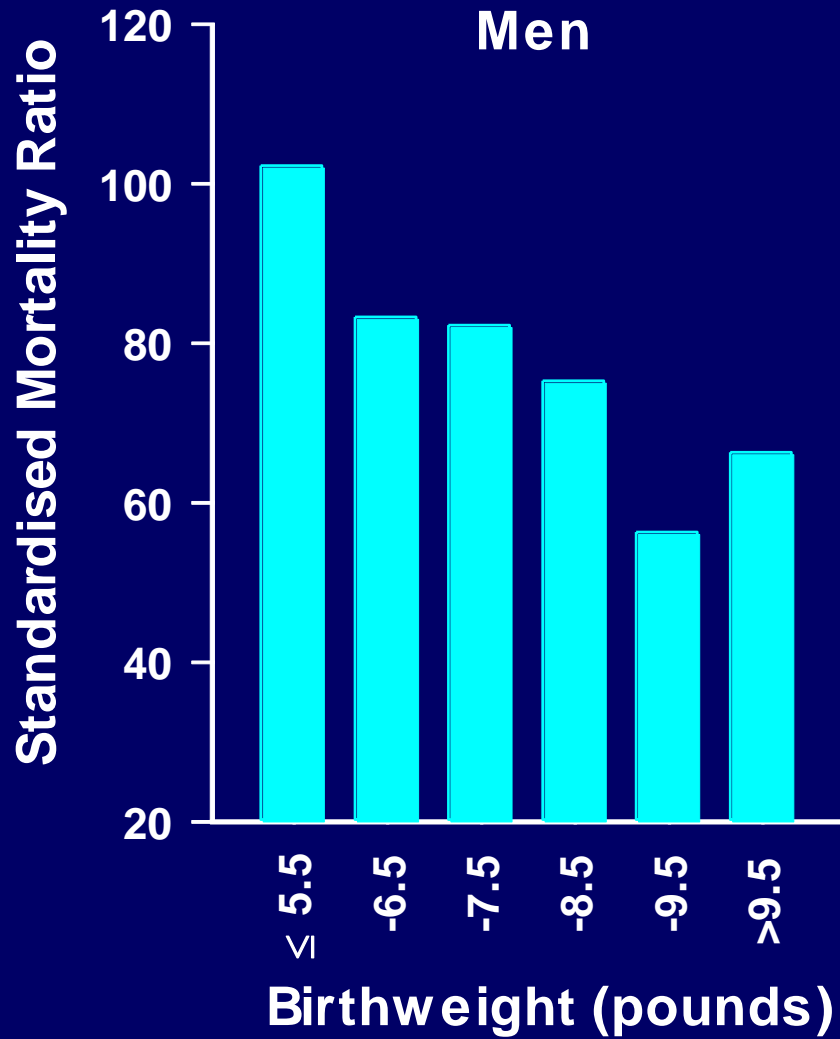


Death rates from Coronary Heart Disease in men 1968-78



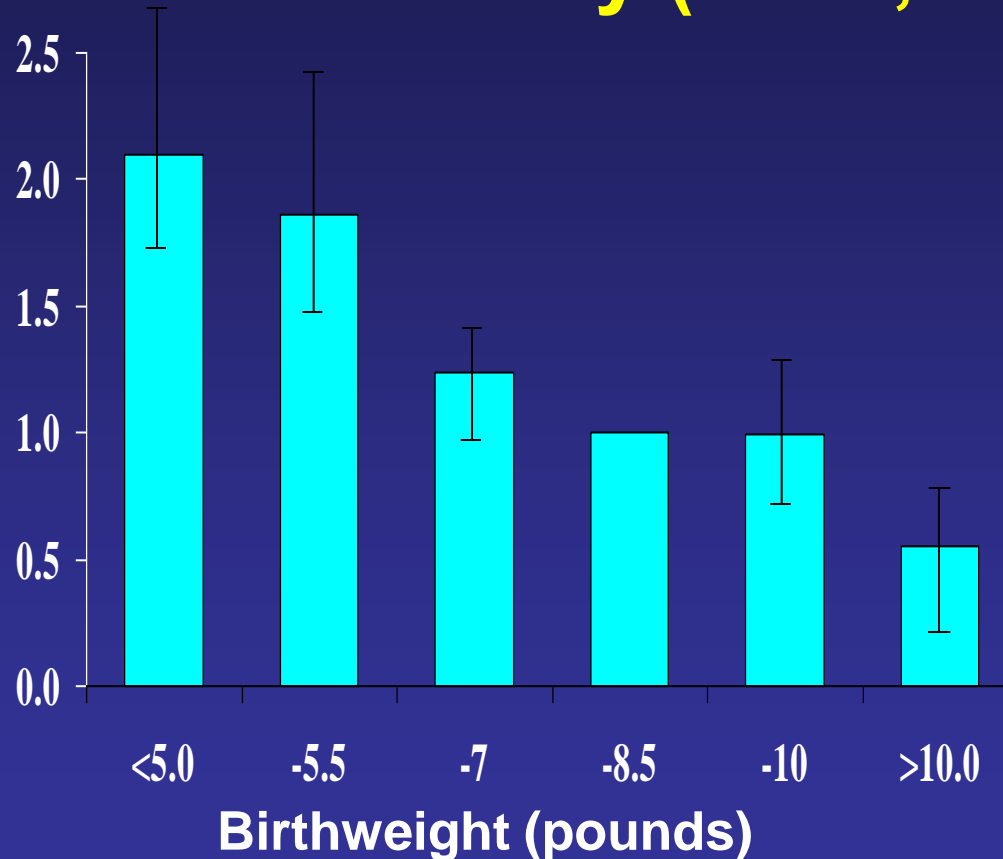


Mortality from coronary heart disease in 15726 men and women in Hertfordshire

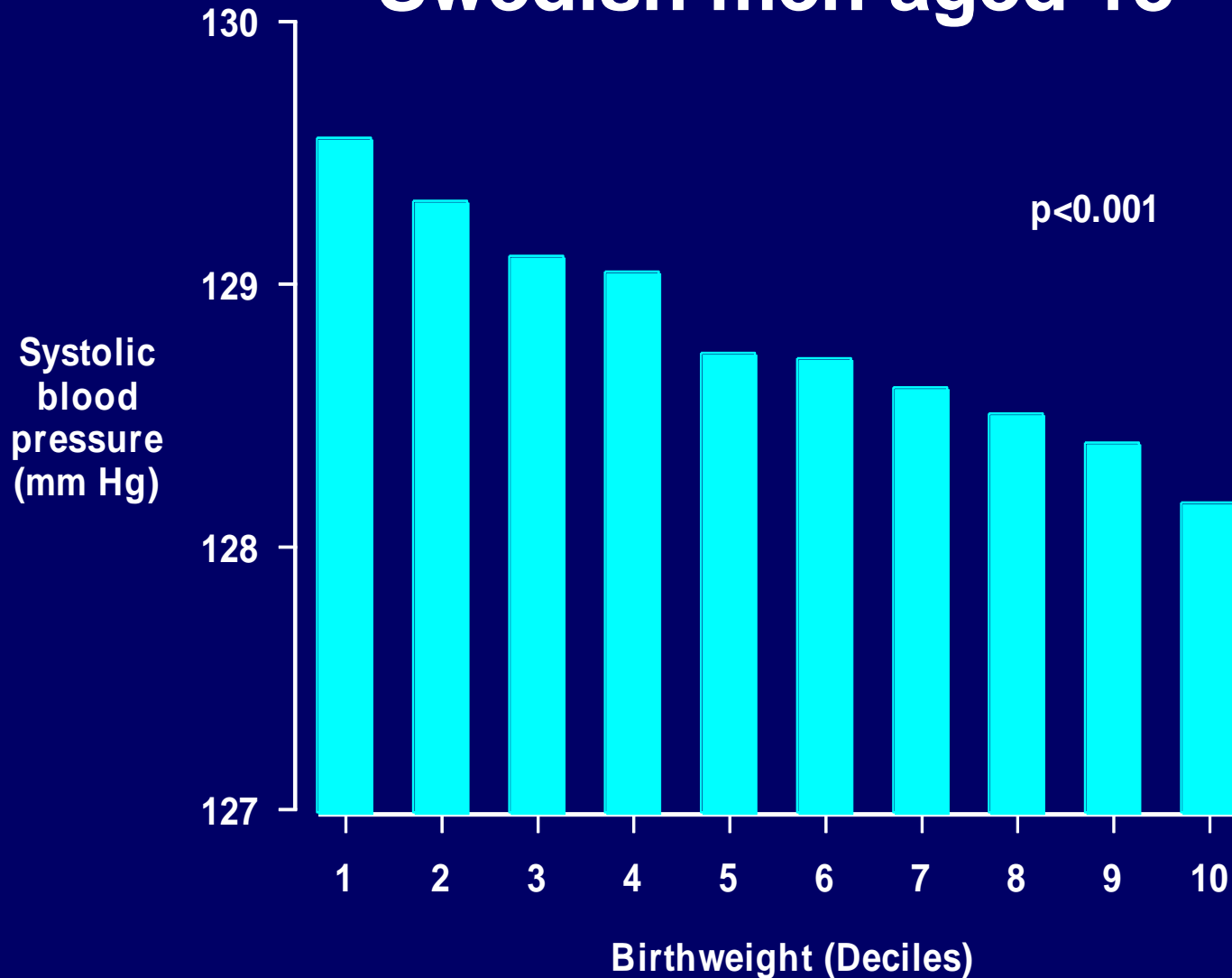


Relative risk of type 2 diabetes

US Nurses' Study (n=69,526)



The relation between systolic blood pressure and birthweight in 149,378 Swedish men aged 18

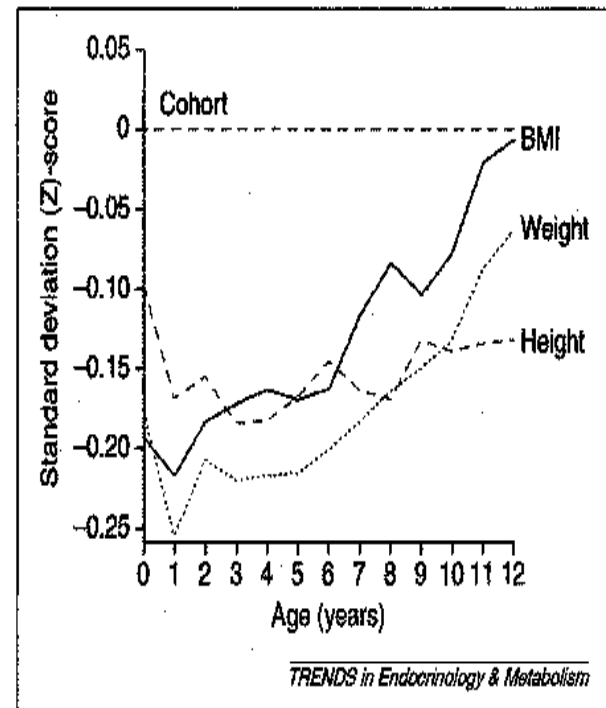


Fetal programming of coronary heart disease

David J.P. Barker

People who develop coronary heart disease grow differently from other people both *in utero* and during childhood. Slow growth during fetal life and infancy is followed by accelerated weight gain in childhood. Two disorders that predispose to coronary heart disease, type 2 diabetes and hypertension, are preceded by similar paths of growth. Mechanisms underlying this are thought to include the development of insulin resistance *in utero*, reduced numbers of nephrons associated with small body size at birth and altered programming of the micro-architecture and function of the liver. Slow fetal growth might also heighten the body's stress responses and increase vulnerability to poor living conditions in later life. Coronary heart disease

The search for the causes of coronary heart disease has hitherto been guided by a 'destructive' model.



Predictive Adaptive Responses

- Processes by which the environmental interactions in early development lead to changes in physiological and physical development, not primarily for immediate advantage, but for expected future advantage in a particular predicted adult environment.

The Fetal Matrix
Gluckman and Hanson

FETAL ORIGIN OF ADULT DISEASE

*Birth weight/
Birth phenotype
Early postnatal
growth*



Adult life

Hypertension

*Ischaemic heart
disease*

Obesity

Insulin resistance

Type 2 diabetes

*Prenatal
stress*



Adult life

Behaviour

Cognition

Memory

Learning

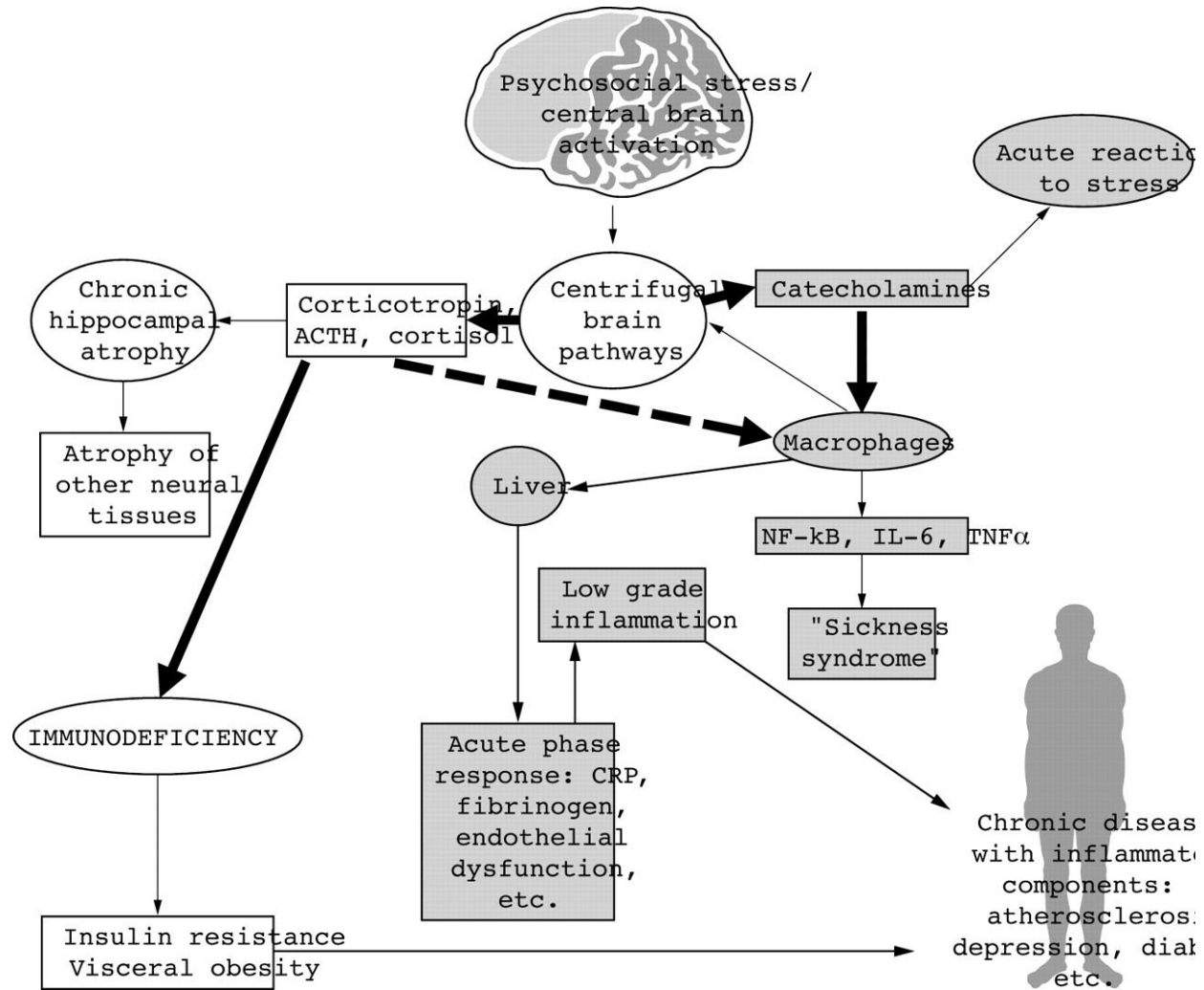
Emotion

Stress Response

What is stress?

- Anxiety and depression/mental illness
- Bad relationship with partner (emotional or physical abuse)
- Lack of social support-not much supportive contact with family or friends
- Recent immigrant/ethnic minority,
- Poverty/bad housing

“The components of the “stress response””.



Vale S Postgrad Med J 2005;81:429-435



The mother's emotional state in pregnancy can have a long lasting effect on her child



- Women have more symptoms of depression and anxiety during pregnancy than postnatally
- Pregnancy can also be a time of increased domestic abuse and relationship strain

More than one million children in UK suffer from neurodevelopmental disorders

- Emotional disorder (anxiety and depression) (4%)
- Conduct disorder (6%)
- Hyperkinetic and/or attention disorder (ADHD) (2%)
- Other e.g autism (1%)
- **Boys 11% girls 8%**



Long term effects of prenatal stress on neurodevelopment

Animal studies.



Wide range of effects on offspring with prenatal stress

- More anxiety
- Reduced attention
- Learning deficits
- Reduced laterality
- Altered sexual behaviour
- Effects different on male and female offspring

- Mediated by HPA axis and cortisol/corticosterone in both mother and offspring

Effect of Stress During Pregnancy on the Adult Offspring Rat.

Stressed dam



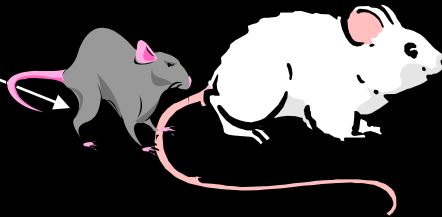
Control dam



Control dam



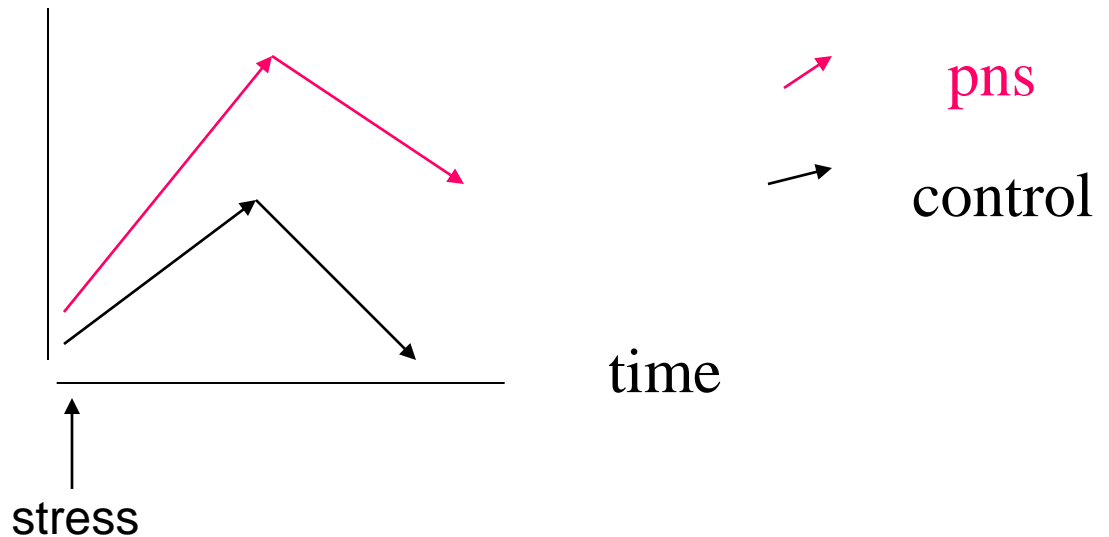
offspring



All offspring were fostered on the 1st day after birth to non-stressed dams

Plasma corticosterone

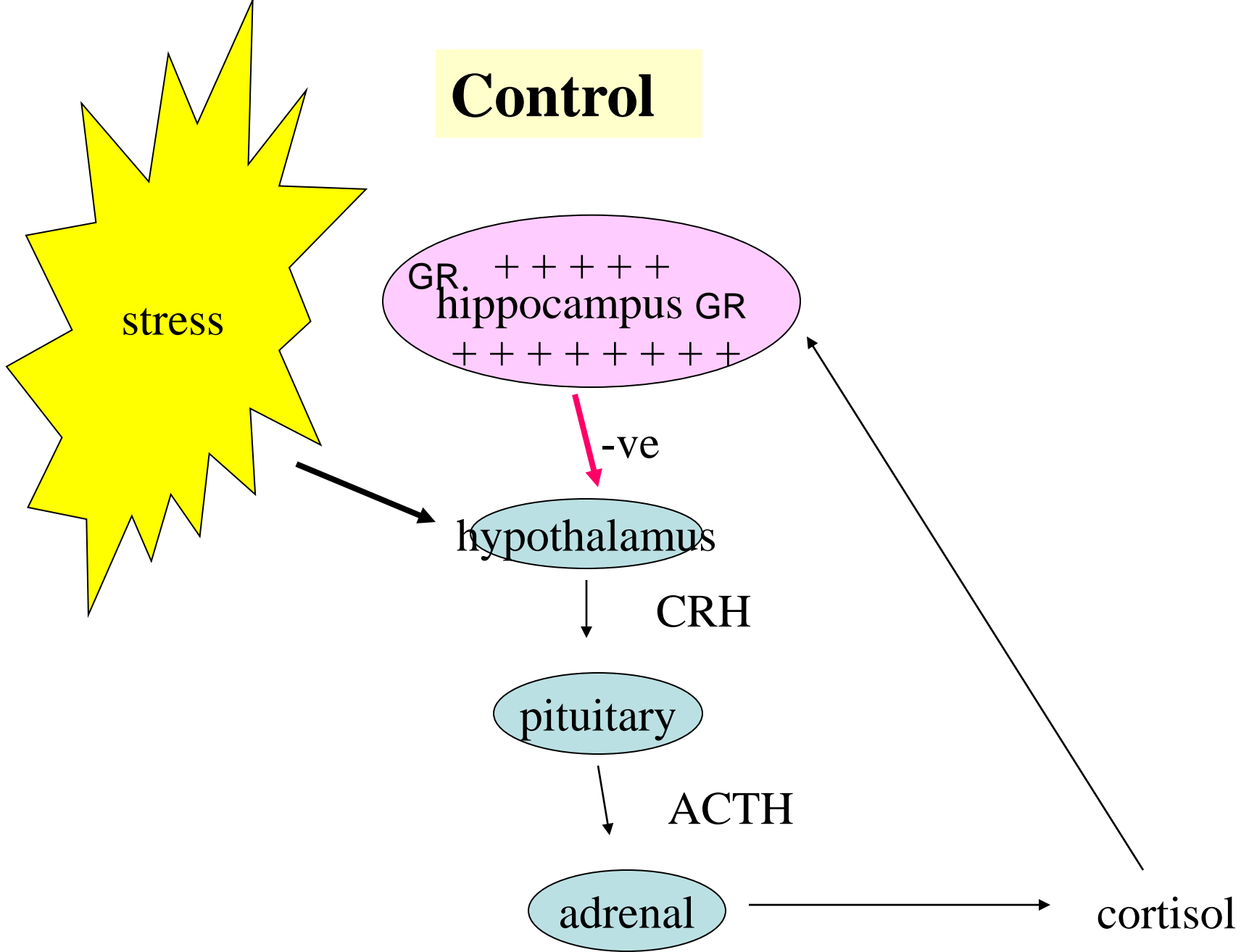
Offspring



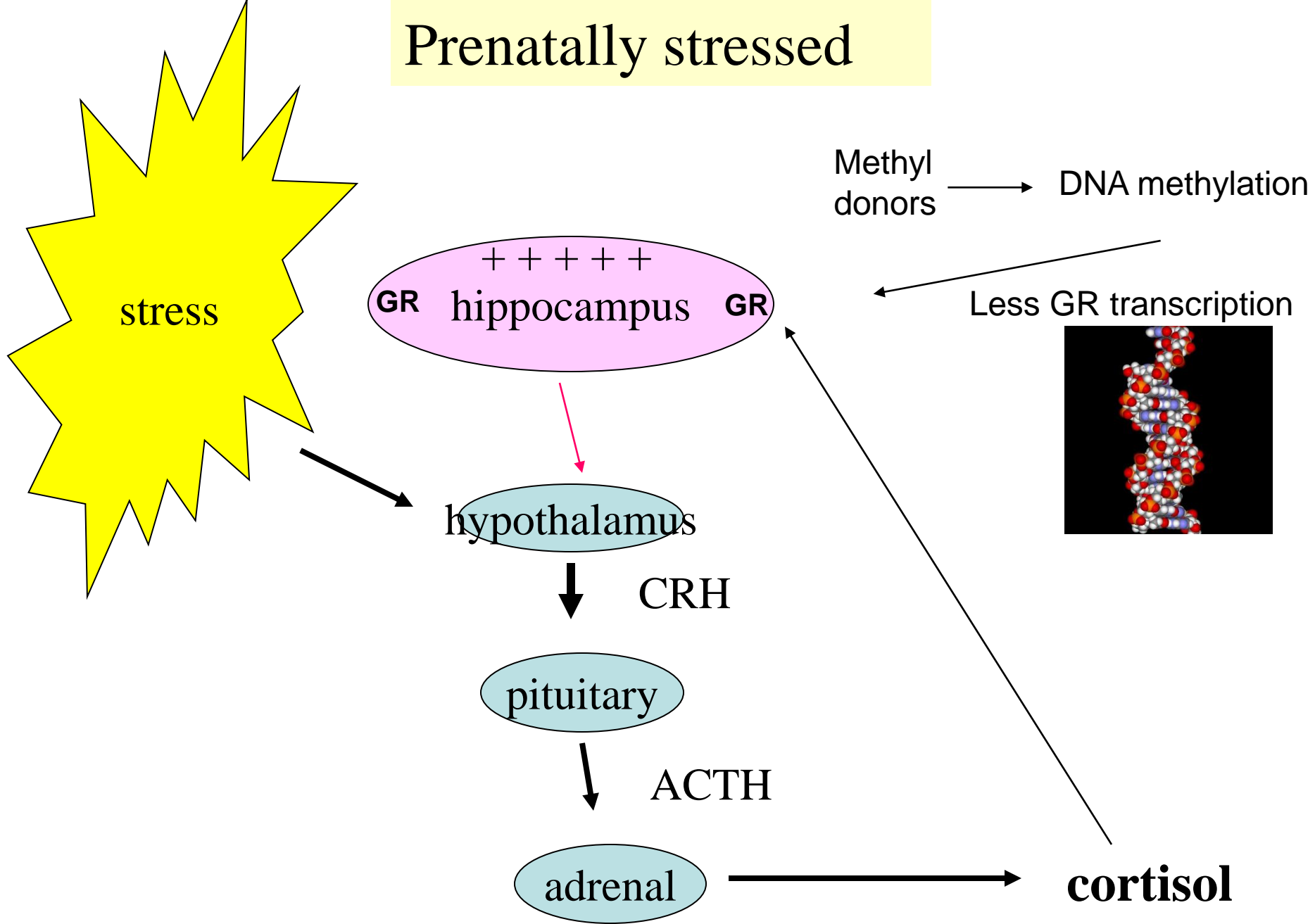
Prenatally stressed animals showed greater and prolonged corticosterone response to novelty stressor

Behave in a more anxious way

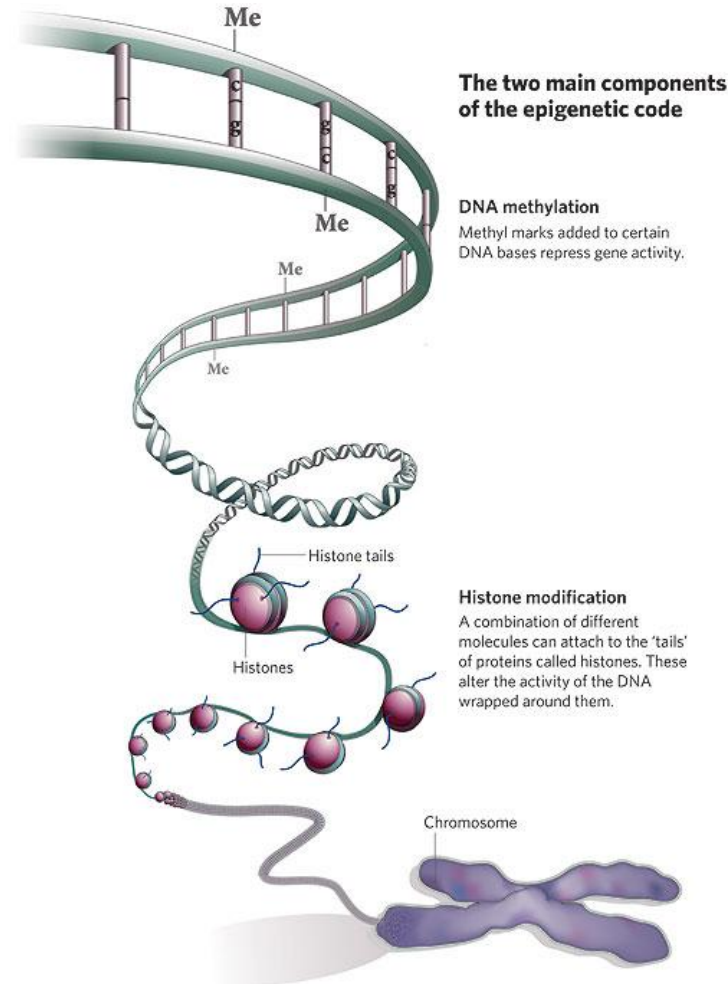
Control



Prenatally stressed



Epigenetic modifications-basis for fetal programming



Epigenetic changes are functionally relevant modifications to the genome that do not involve a change in nucleotide sequence. Can persist to grandchild generation



Human studies

Examples of prenatal stress reported to cause changes in development and behavior

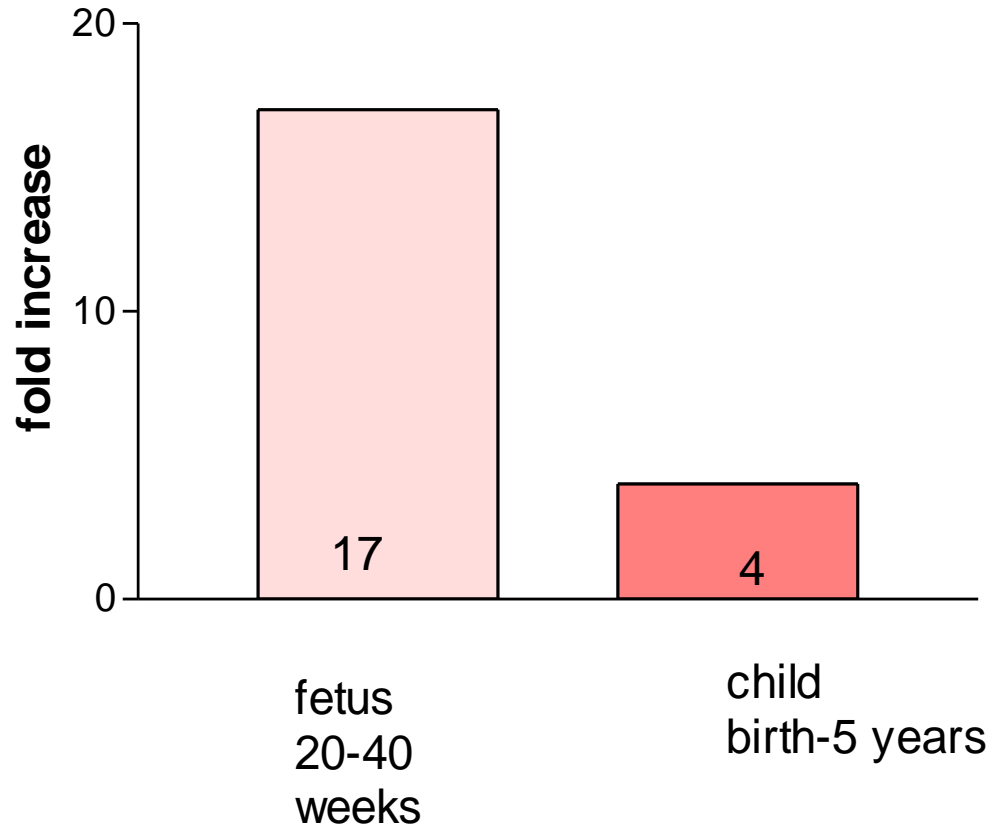
- Maternal anxiety and depression
- Maternal daily hassles
- Pregnancy specific anxiety
- Partner or family discord
- Distress caused by 6 day war in Israel, 1967
- Experience of acute disasters, e.g. freezing ice storm, hurricane or 9/11

- It's not just extreme stress

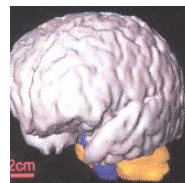
Antenatal stress in humans associated with increased incidence of :

- Anxiety and Depression
- Behavioural problems-ADHD, conduct disorder
- Impaired cognitive development, especially of language
- Mixed handedness
- Sleep problems in infants
- Autism?
- Schizophrenia?
- Asthma

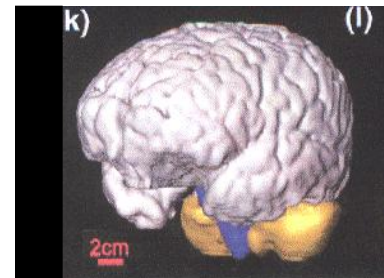
Relative increase in brain size



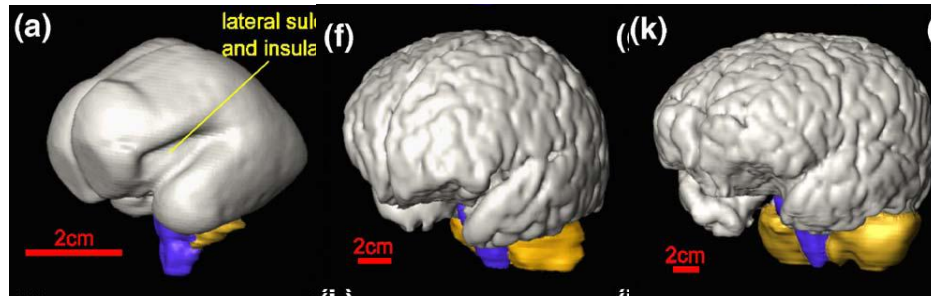
20 week fetus



birth



5 years

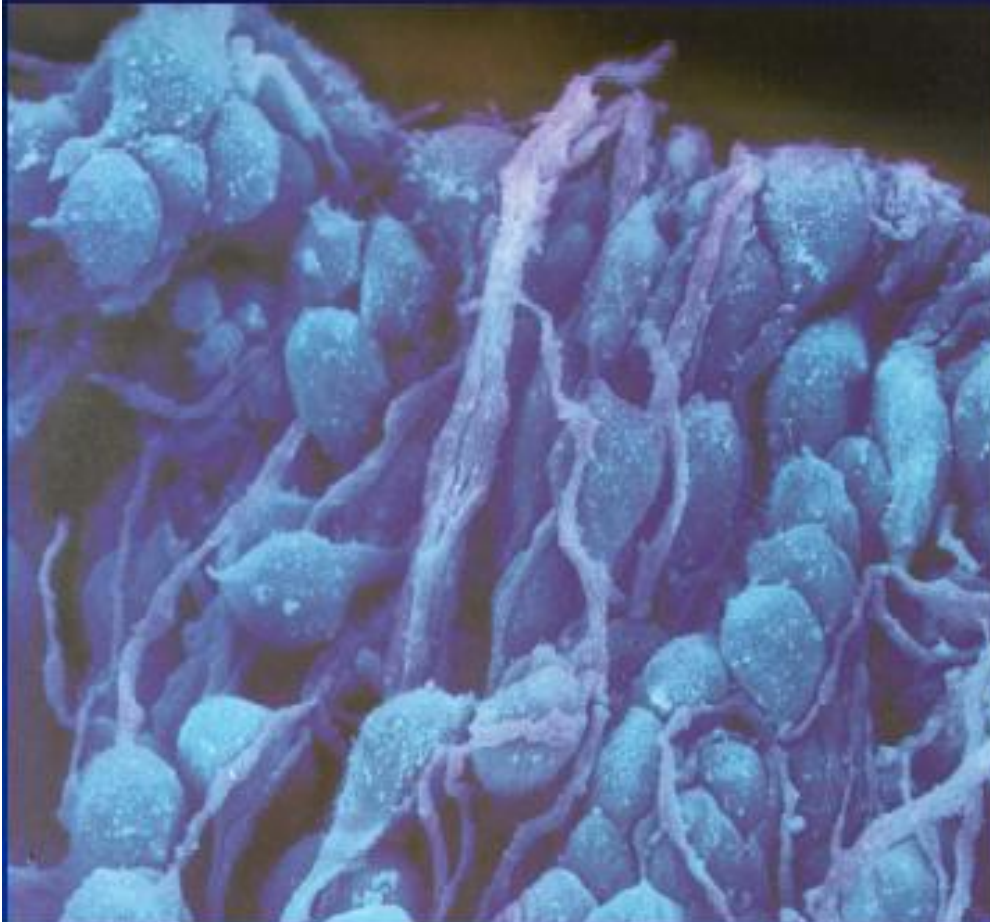


19 weeks

Term

5-6years

The Fetal Brain is “Under Construction”



- 3 mm long neural tube – whole brain with 100 billion neurons and 100 trillion connections
- 250,000 neurons/minute – all through gestation
- **Proliferation:** 5 wks gestation through 18 months after birth
- **Migration**
- **Differentiation**
- **Synaptogenesis**
- **Neural pruning:** continues till puberty...

ALSPAC Study. Does antenatal stress affect child behaviour in humans?

- Aim of our study:
- To determine the long term effects of antenatal stress or anxiety on the behavioural development of the child

Fetus age 20 weeks (18cm)



ALSPAC

Avon Longitudinal Study of Parents and Children

- Large prospective birth cohort
~14,000 pregnant women
recruited around Bristol in
1990-1991



- Detailed information on children at 4, 7, 11, 13 and 15 years

ALSPAC study



Maternal anxiety-at 18 and 32 weeks of pregnancy
Compared 15% most anxious mothers
with the rest

Child behaviour

–maternal report at 4 and 7 years old.
Strengths and Difficulties questionnaire.
Attention deficit/hyperactivity;
anxiety and depression;
conduct disorder

O'Connor et al 2002, 2003

Multivariate Analysis

Cohort with complete data
 $n = 7,363$

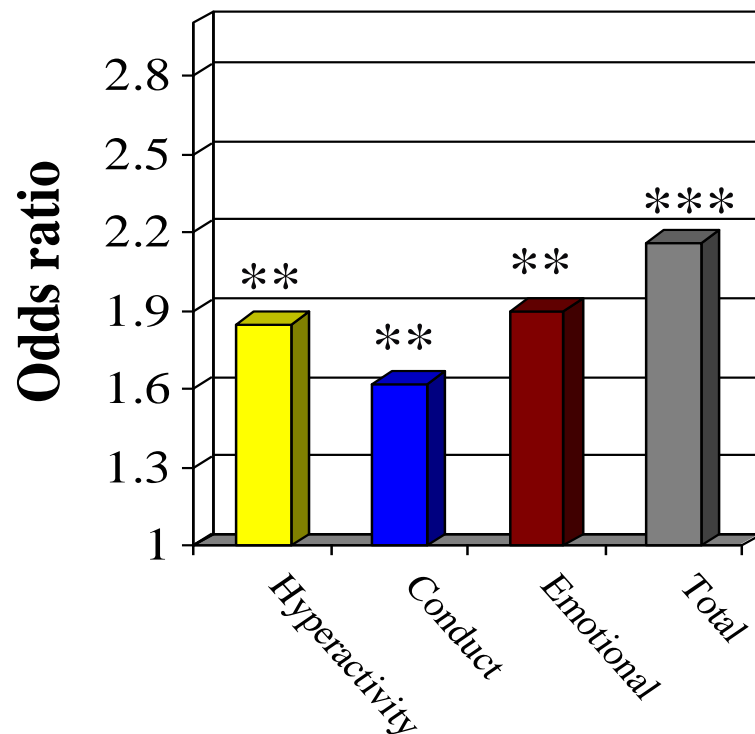


- Postnatal anxiety and depression
- Maternal age
- Birthweight
- Gestational age
- Smoking
- Alcohol
- Psychosocial factors: crowding
- Maternal education

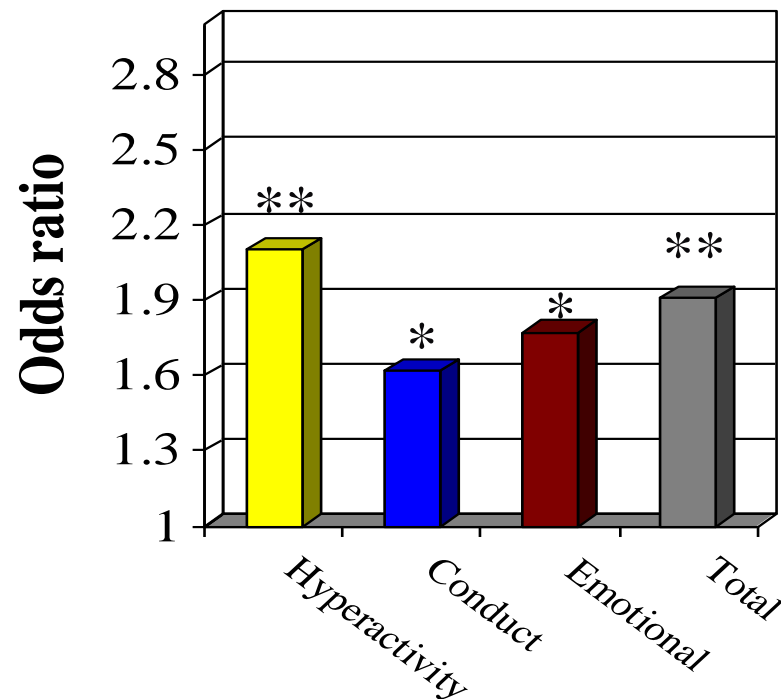
Multivariate analysis–ALSPAC cohort at 7 years

Behavioural/emotional problems and maternal antenatal anxiety at 32 weeks

BOYS



GIRLS



- For top 15% of most anxious women in pregnancy, SDQ symptom rate
- (ADHD, anxiety, conduct disorder)
- in 4 and 7 year old children
- doubled from 5 to 10% (after multivariate analysis).

- Attributable load of behavioural/emotional problems in whole population due to antenatal anxiety/stress ~10-15%



Links are similar with antenatal anxiety at 18 weeks gestation but less marked than anxiety at 32 weeks

Links are similar with depression but not as strong as anxiety

It is not just first trimester

Other ALSPAC studies

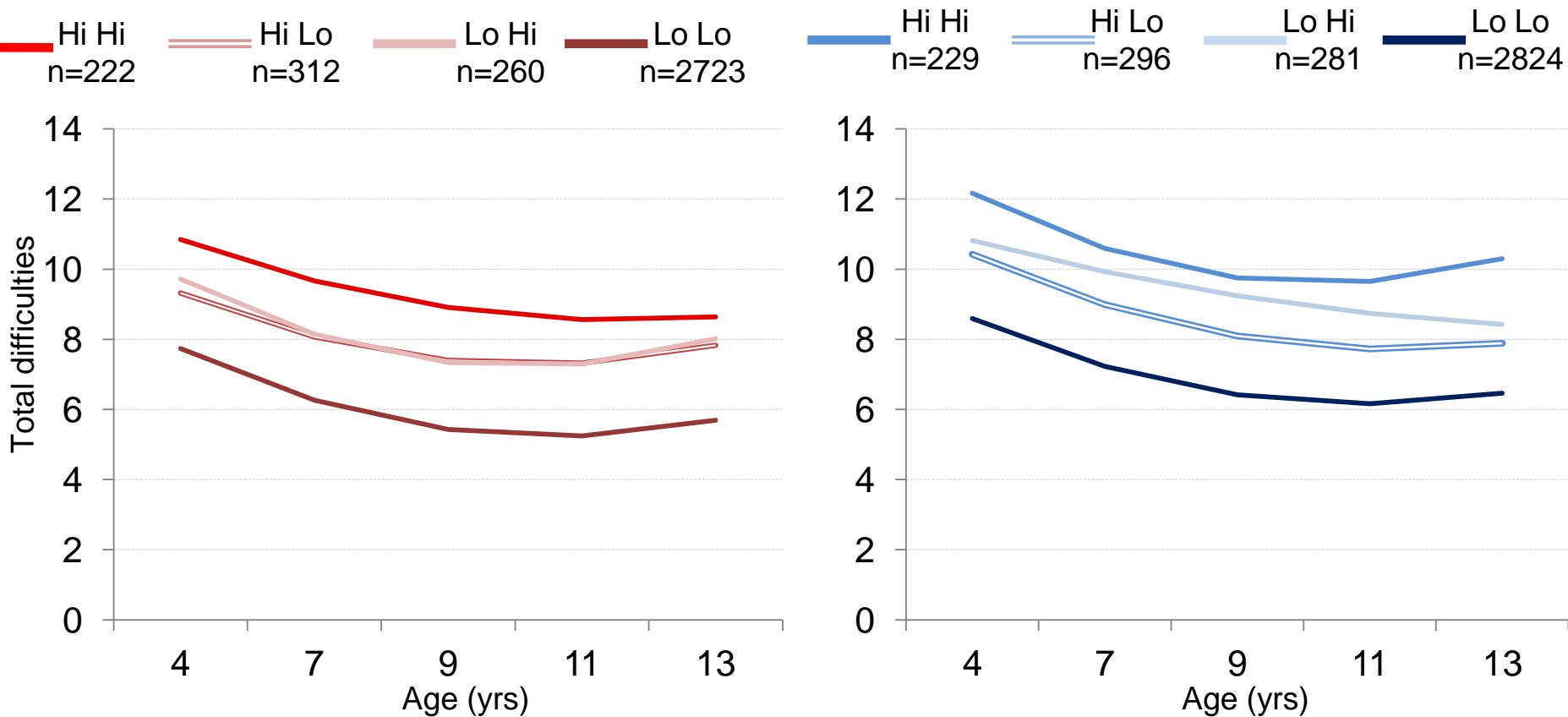


Maternal antenatal anxiety
associated with:

- Increased mixed handedness
- More sleep problems in infancy
- Increased child cortisol at 10 years but not at 15 years

Total SDQ scores and maternal anxiety at 32 weeks Prenatal and 33 months Postnatal

-allowing for BW, GA, maternal age, maternal education, SES, maternal substance use, parenting, etc



Amniocentesis study



- Women recruited at time of amniocentesis (mean 17.2 weeks GA)
- Maternal plasma and amniotic fluid cortisol measured
- Mother and child recalled when child is 17 months, if full term, and no known medical problems (n=126)
- Child: Bayleys tests (MDI) for cognitive development
- Mother and child. Strange Situation test for maternal attachment
- Child saliva (cortisol collected) before and after Strange Situation test.

Spielberger state and trait Anxiety questionnaire

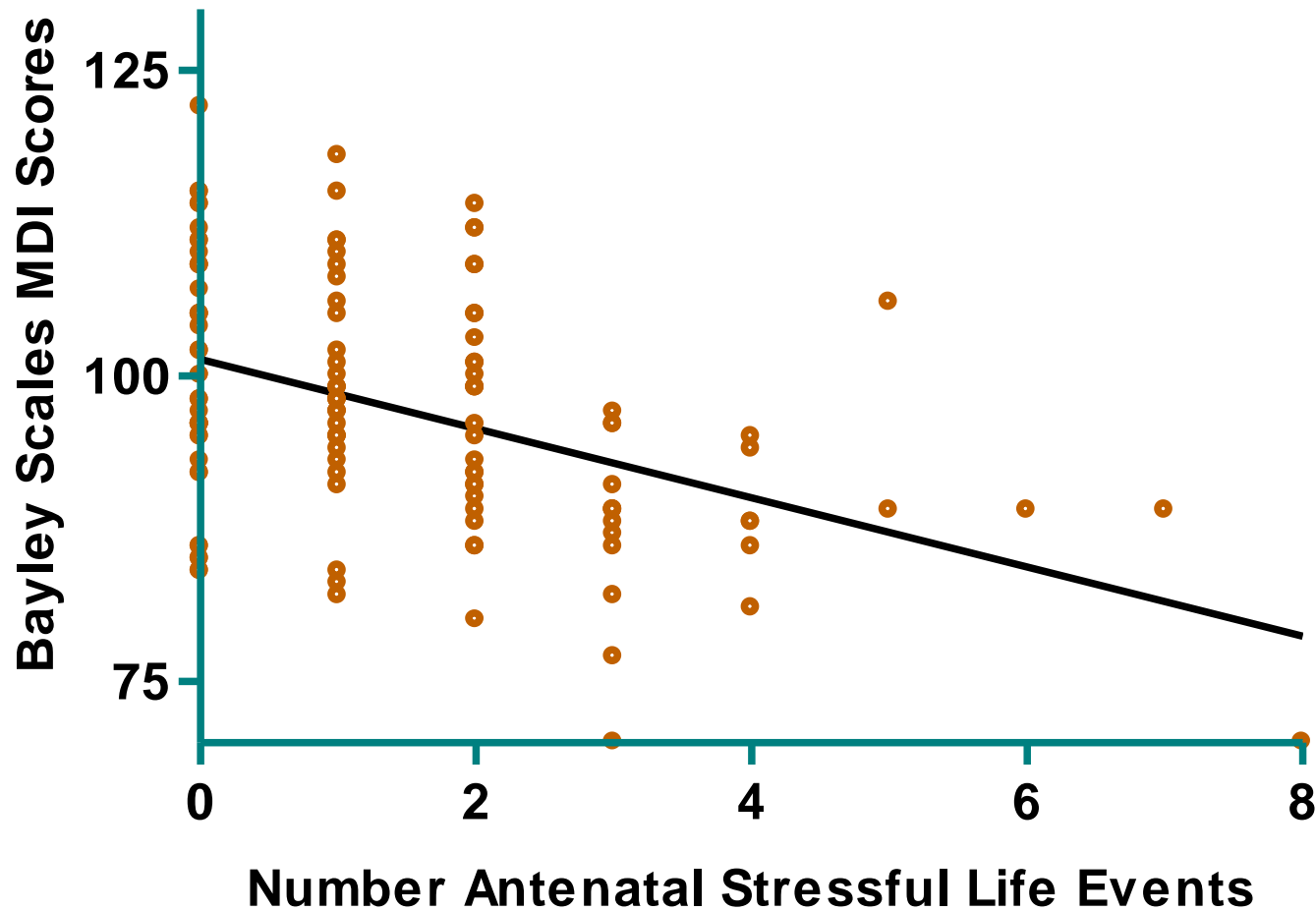


Bayley Scales of Infant Development (BSID-II)

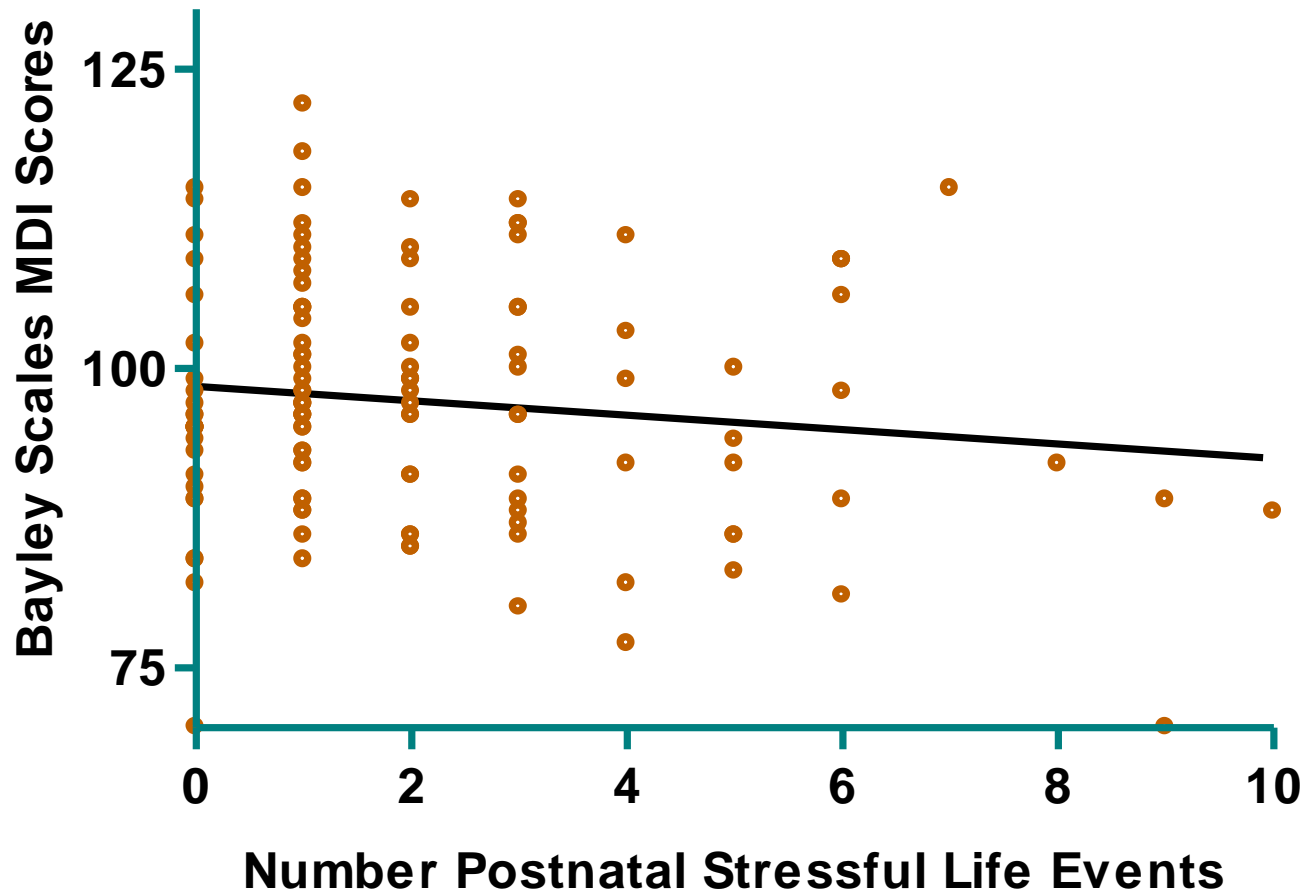


**Study child's
cognitive
(MDI)
development
at
17 months**

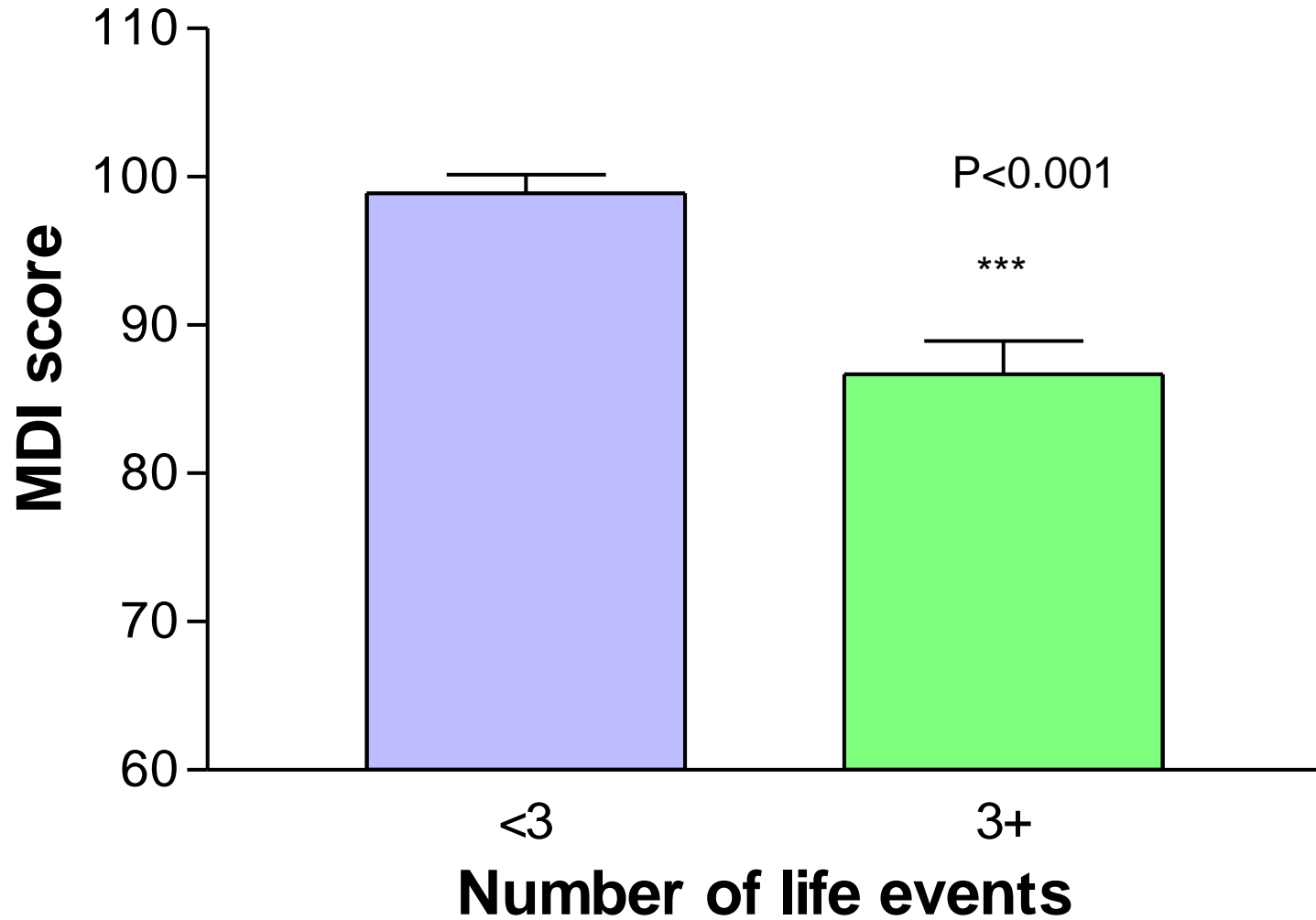
Association between number of antenatal stressful life events and Bayley Scales MDI score at follow-up ($r_s(125)=- 0.39$, $p<0.001$)



Association between number postnatal stressful life events and Bayley Scales MDI score at follow-up ($r_s(125)=-0.05$, ns)



Antenatal life events and Bayley's Mental Development score at 18 months



Significant correlation coefficients between antenatal life event scores and child's MDI

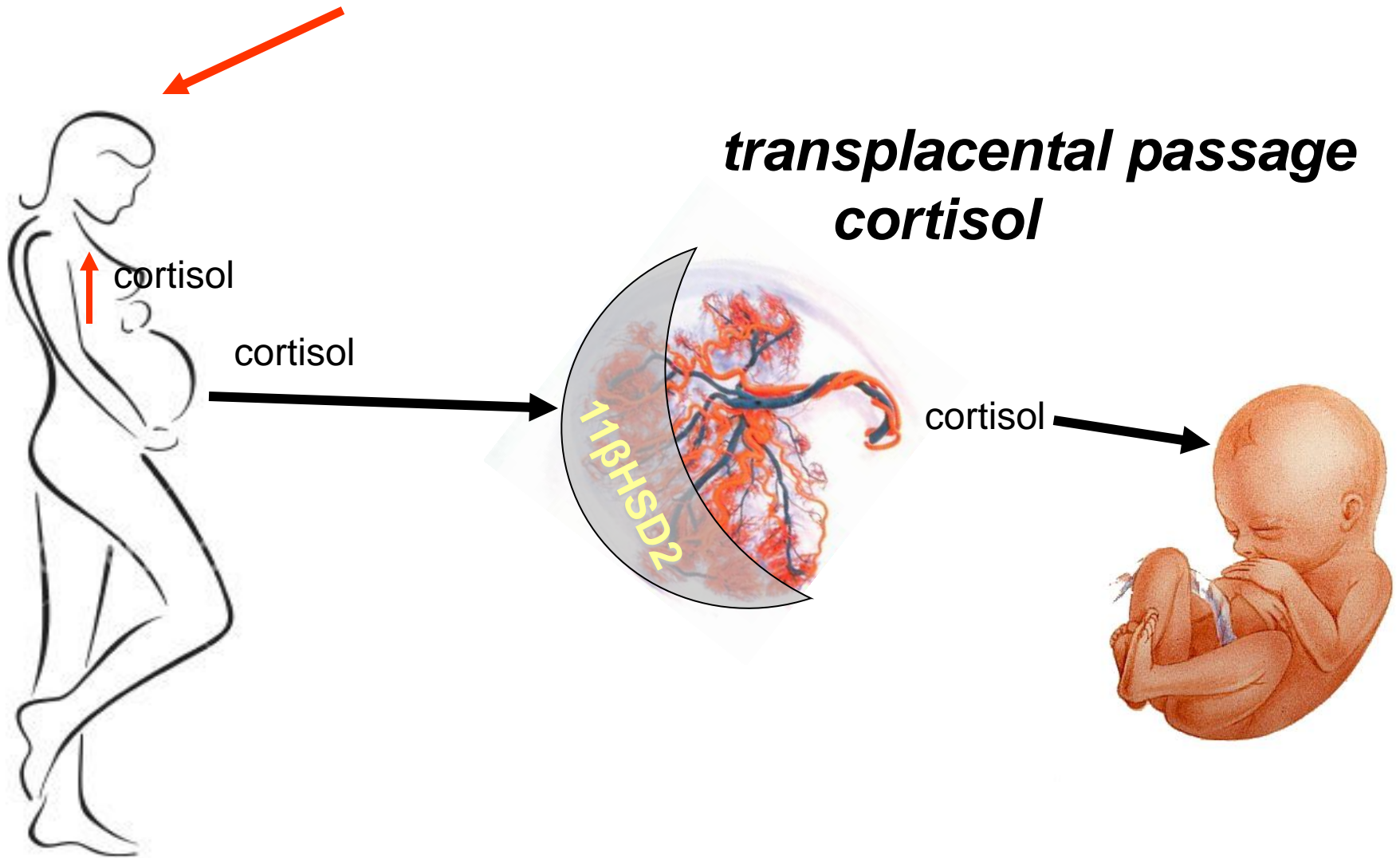
You were separated/divorced	-0.33**
You had a serious argument with your partner	-0.28*
Your partner was emotionally cruel to you	-0.37**
You suffered from mental illness	-0.24*
A friend or relative suffered from mental illness	-0.24*

Multivariate analysis: MDI

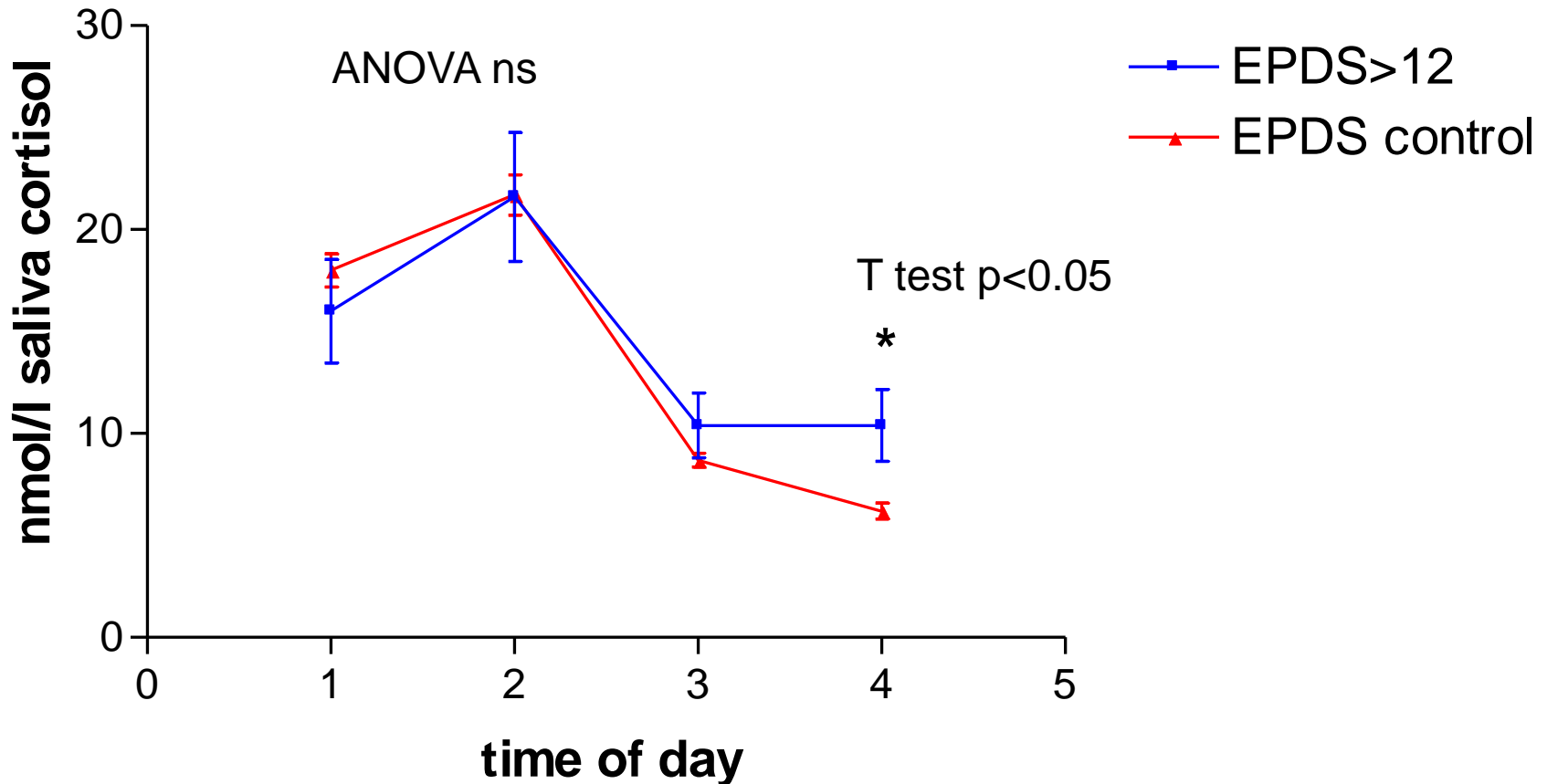
<i>Predictor variables</i>	<i>B</i>	<i>SE</i>	<i>Beta</i>
Maternal education	1.37	0.63	0.19*
Smoking during pregnancy	-2.84	2.21	-.12
Alcohol during pregnancy	0.23	0.55	0.04
Child sex (Female=1; Male=2)	-2.67	1.65	-0.13
Child age	-1.22	0.59	-0.17*
Maternal age	-0.12	0.21	-0.05
Trait anxiety at follow-up	-0.03	0.12	-0.03
Depressive symptoms at follow-up	.06	.27	.03
Social support at follow-up	.04	.12	.03
Prenatal stressful life events	-3.04	0.58	-0.47**
Postnatal stressful life events	0.65	0.47	0.14

How?

Maternal stress/anxiety/mental illness

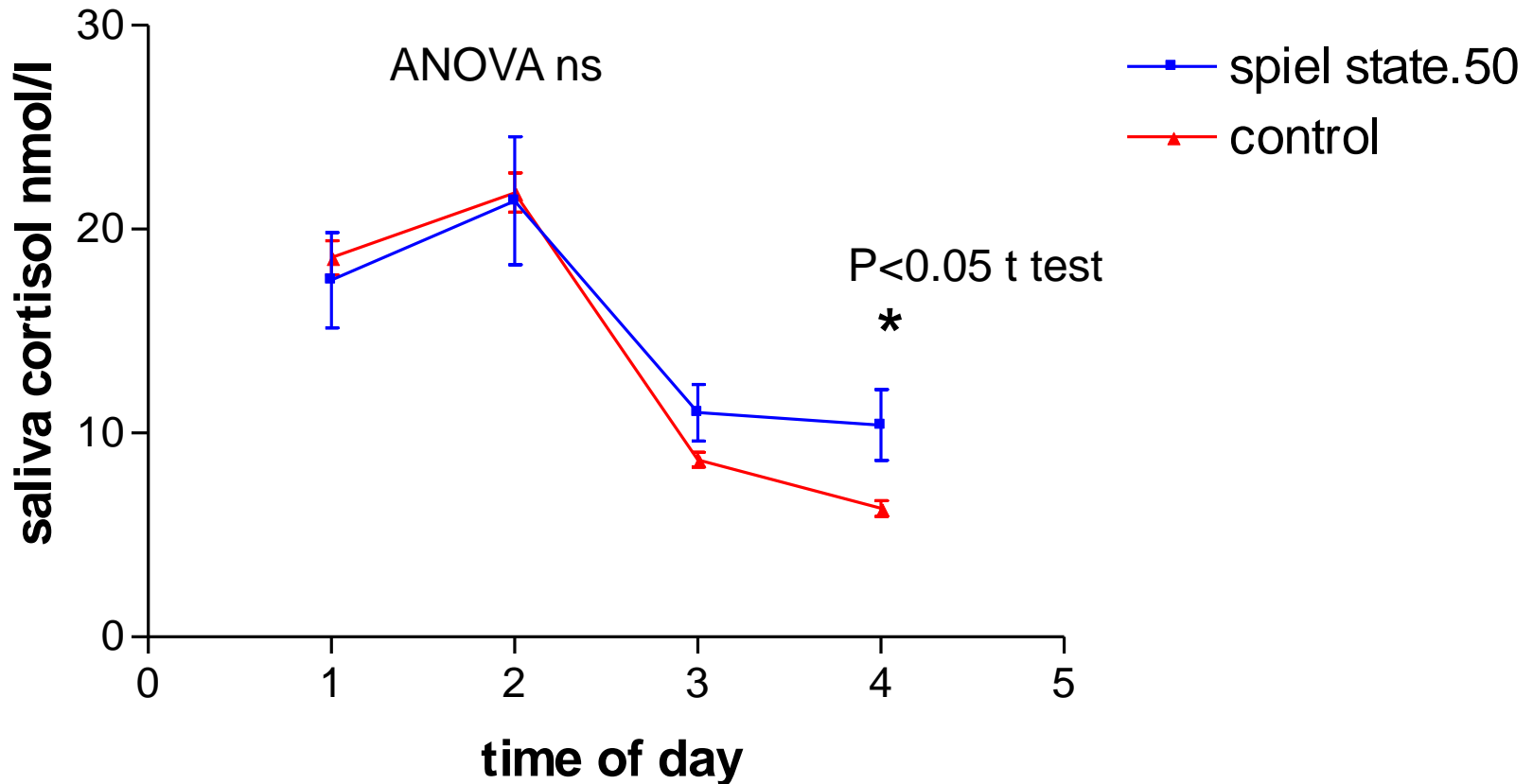


Maternal diurnal cortisol at 32 weeks and EPDS



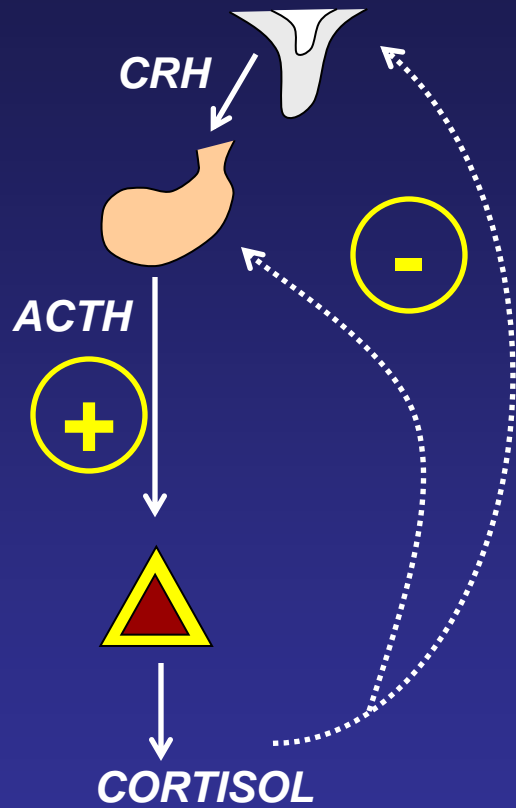
No association between cortisol and EPDS at 20 weeks

Diurnal cortisol at 32 weeks and Spielberger State anxiety

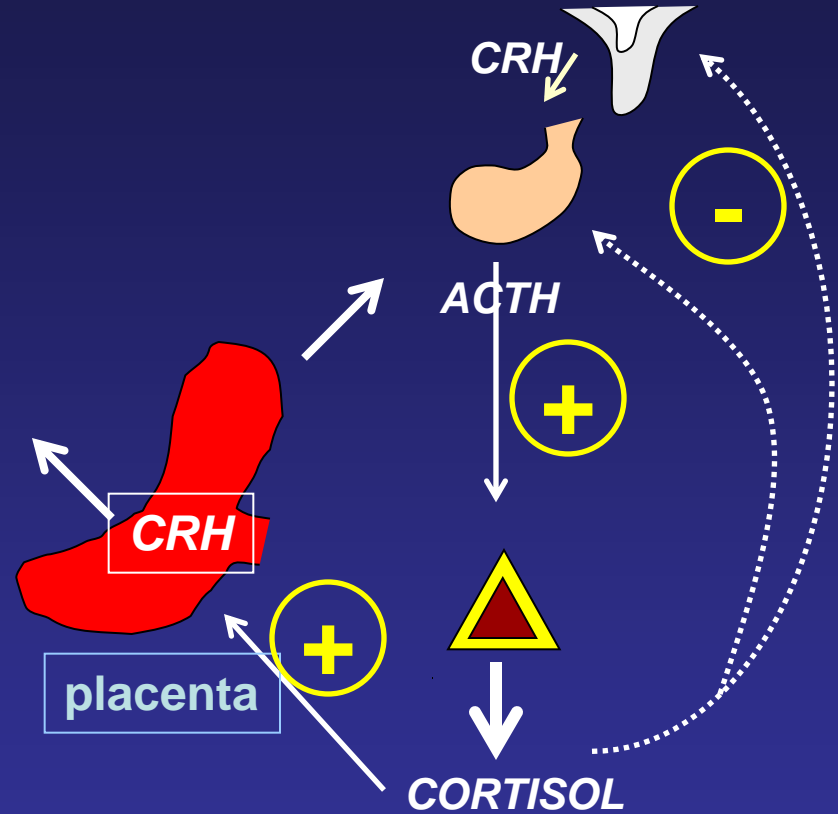


No association between cortisol and anxiety at 20 weeks

Placental CRH in human pregnancy

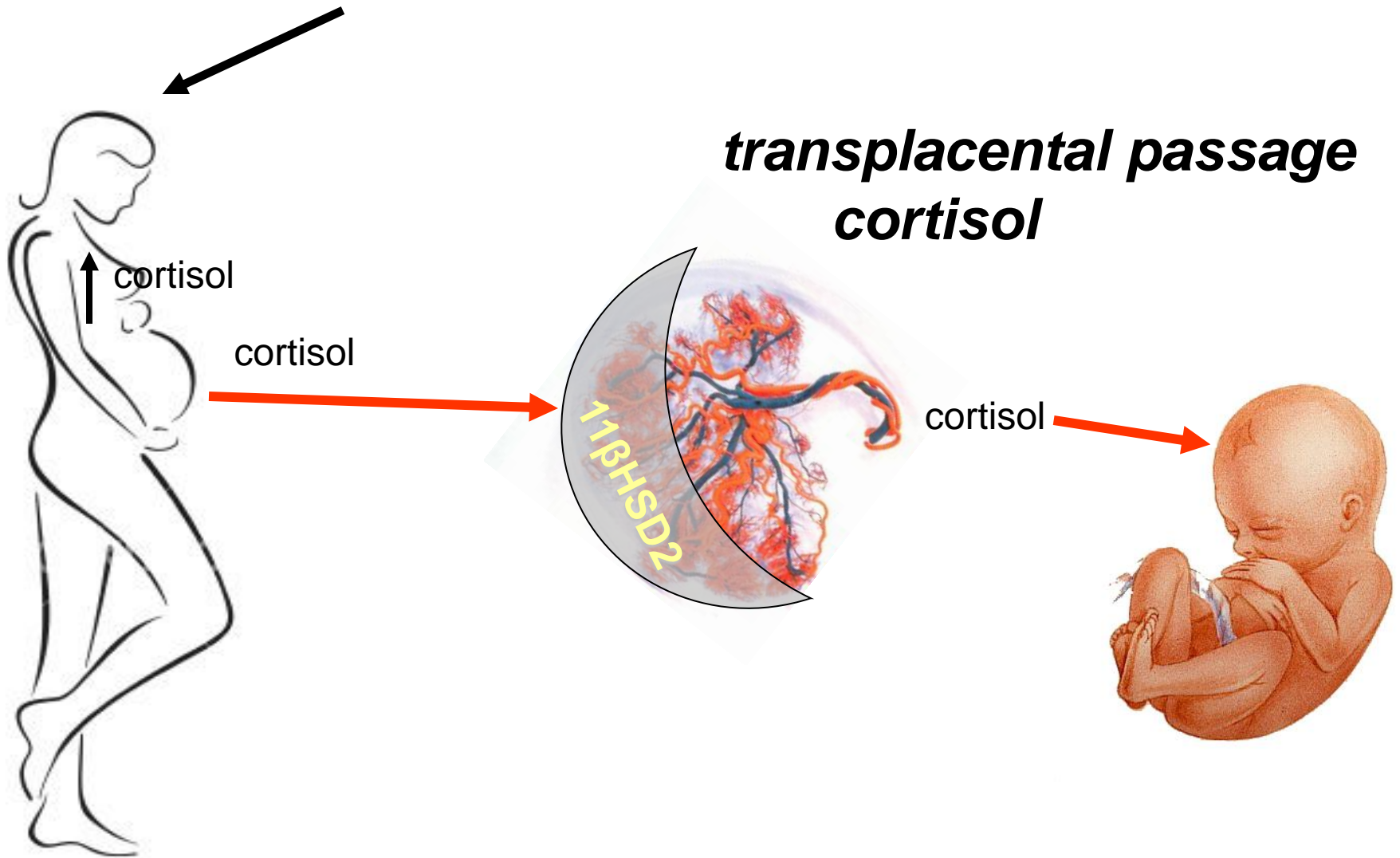


non-pregnant state

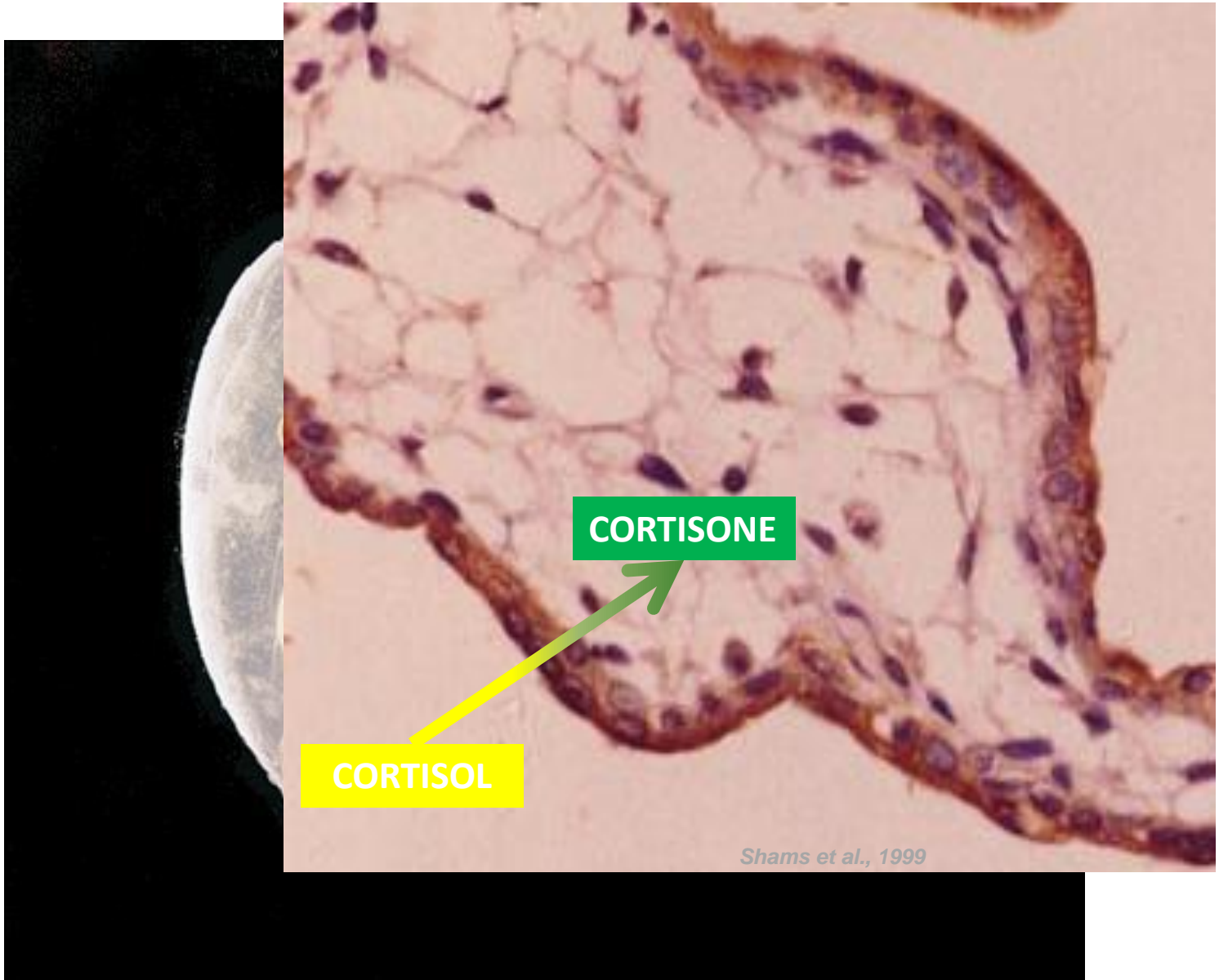


pregnant state

Maternal stress/anxiety/mental illness



The fetal adrenal 11 β HSD2

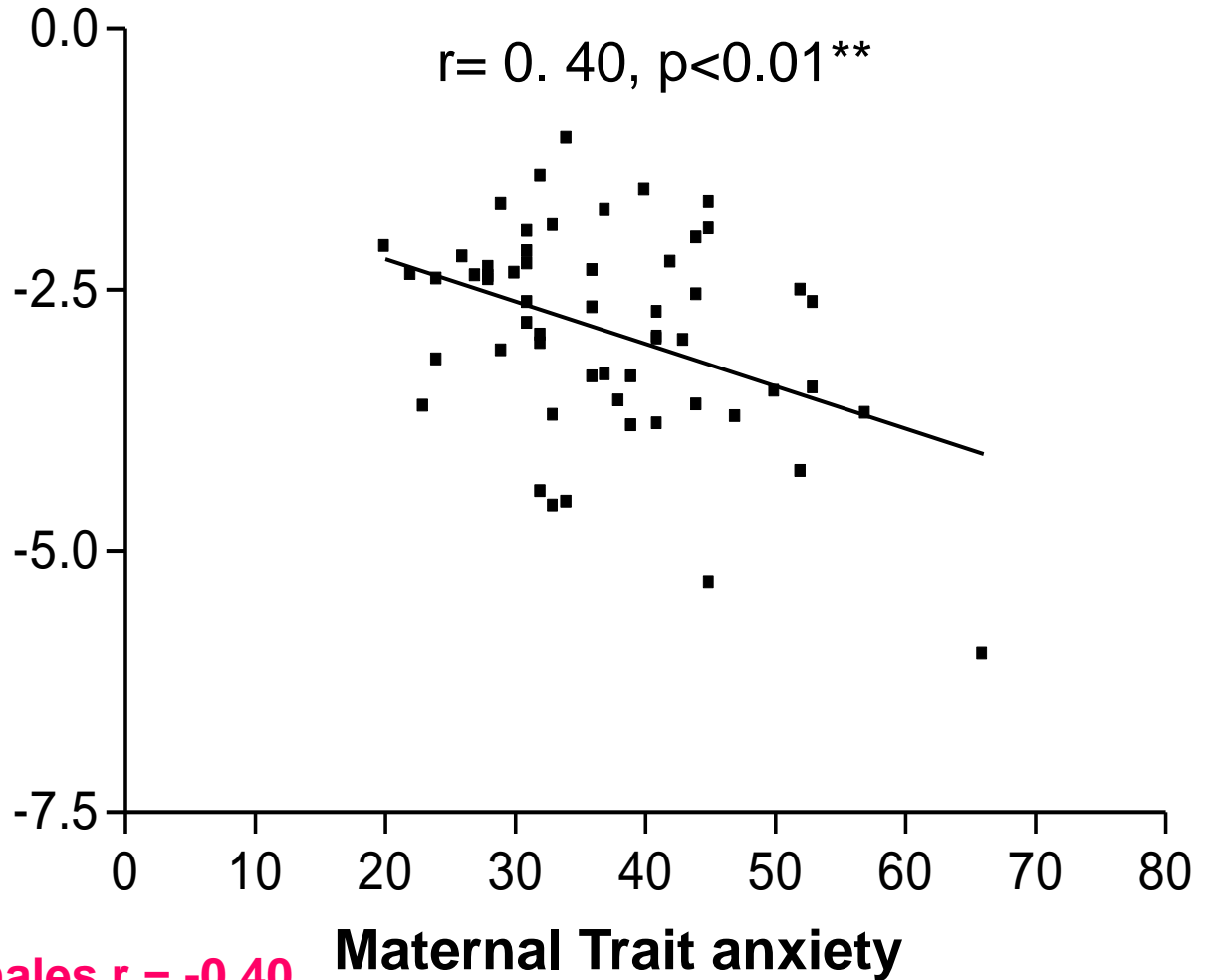
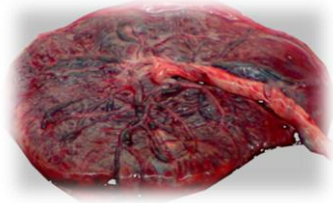


Shams et al., 1999

Placental study

- Recruit women having an elective caesarean, day before
- Exclude medical disorders
- Give psychometric questionnaires including Spielberger Trait Anxiety
- Collect placenta
- Dissect within one hour after delivery -5 pieces at similar depth
- Store at -80°C
- Analyse for 11- β HSD2 mRNA expression

1/11 β -HSD2 Δ CT



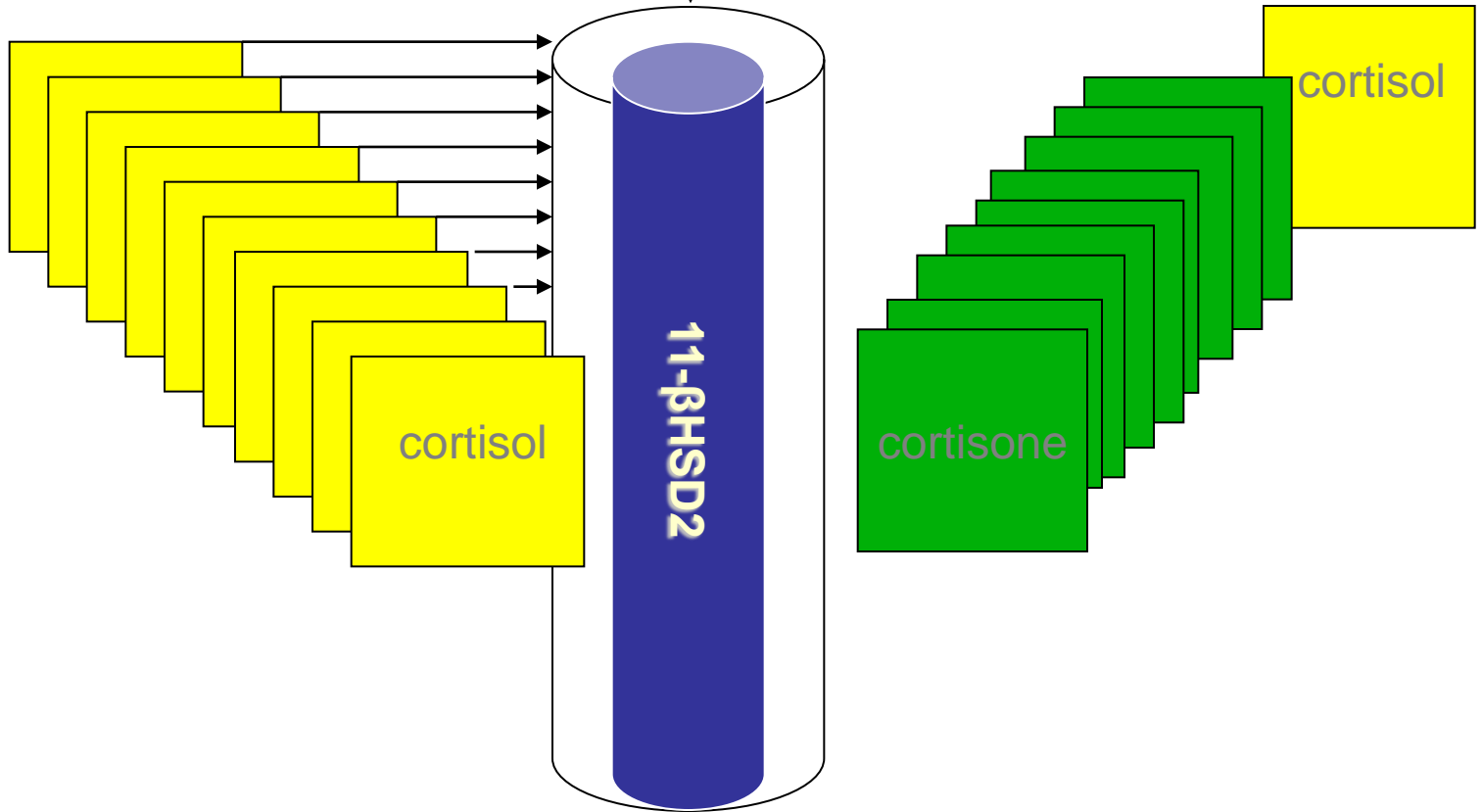
Males $r = -0.39$
 $p = 0.040$
 $n = 28$

Females $r = -0.40$
 $p = 0.034$
 $n = 28$

significant correlation with State anxiety
trend with depression

11- β HSD2

stress



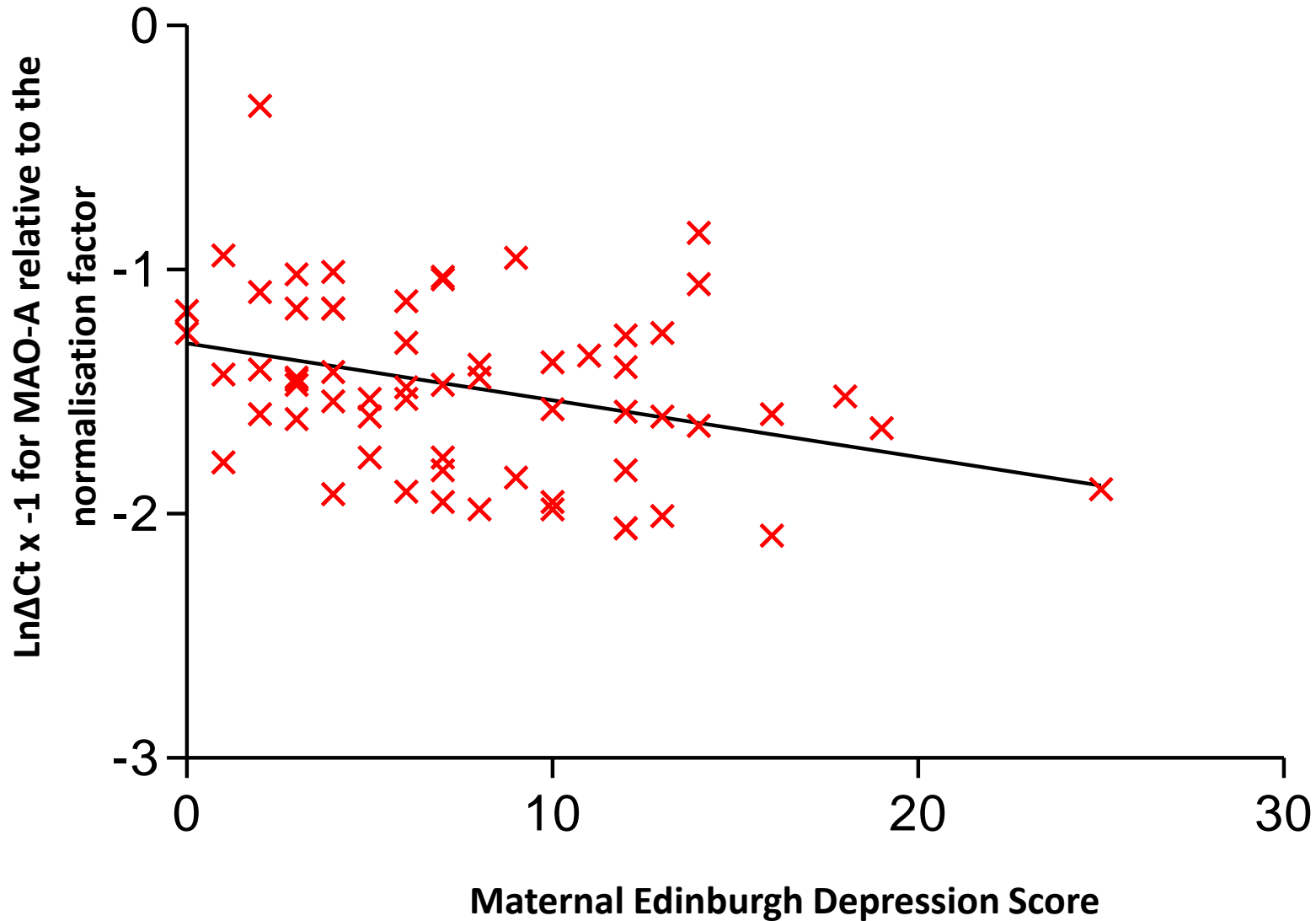
Maternal

Placenta

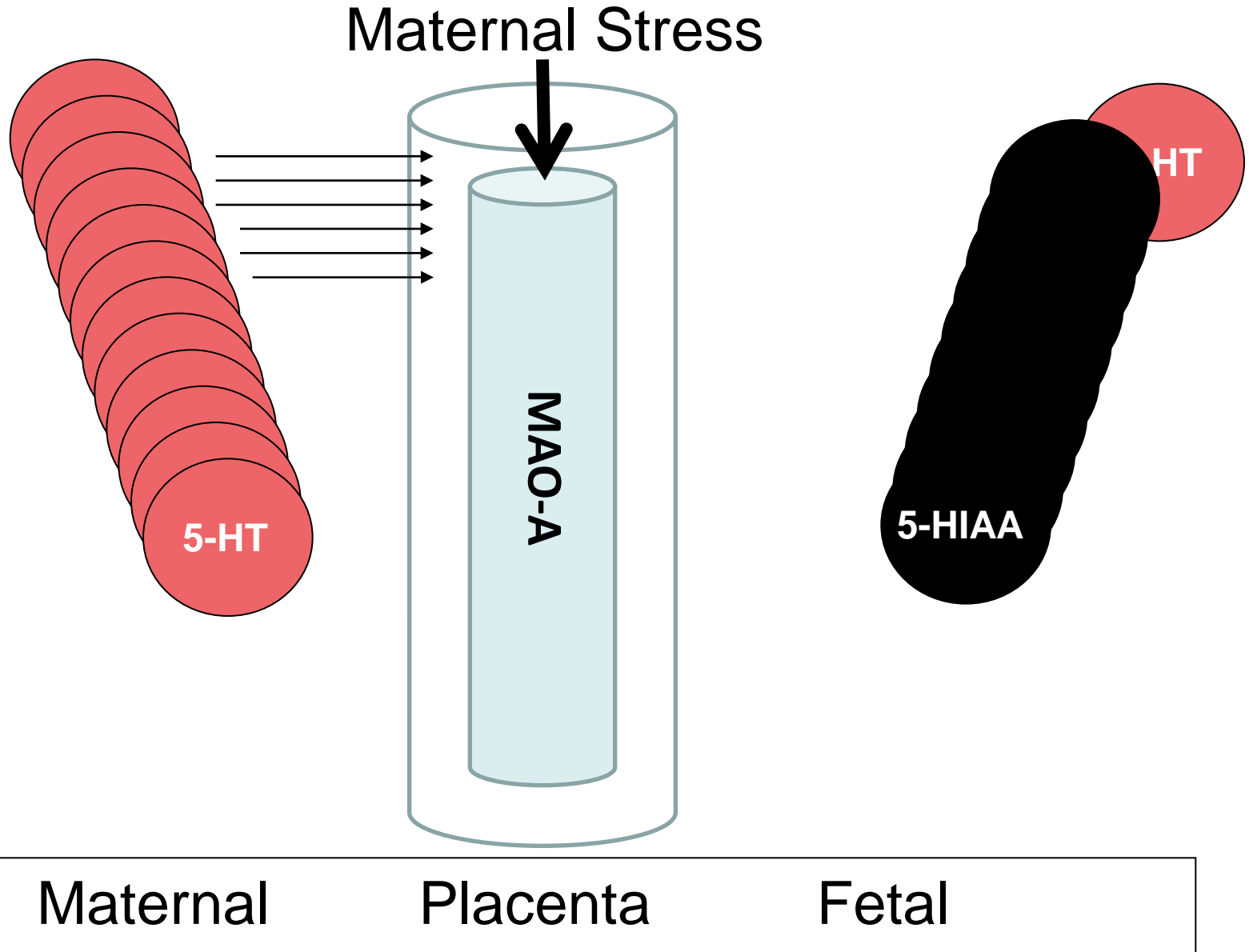
Fetal

Placental MAO-A and Maternal EDS

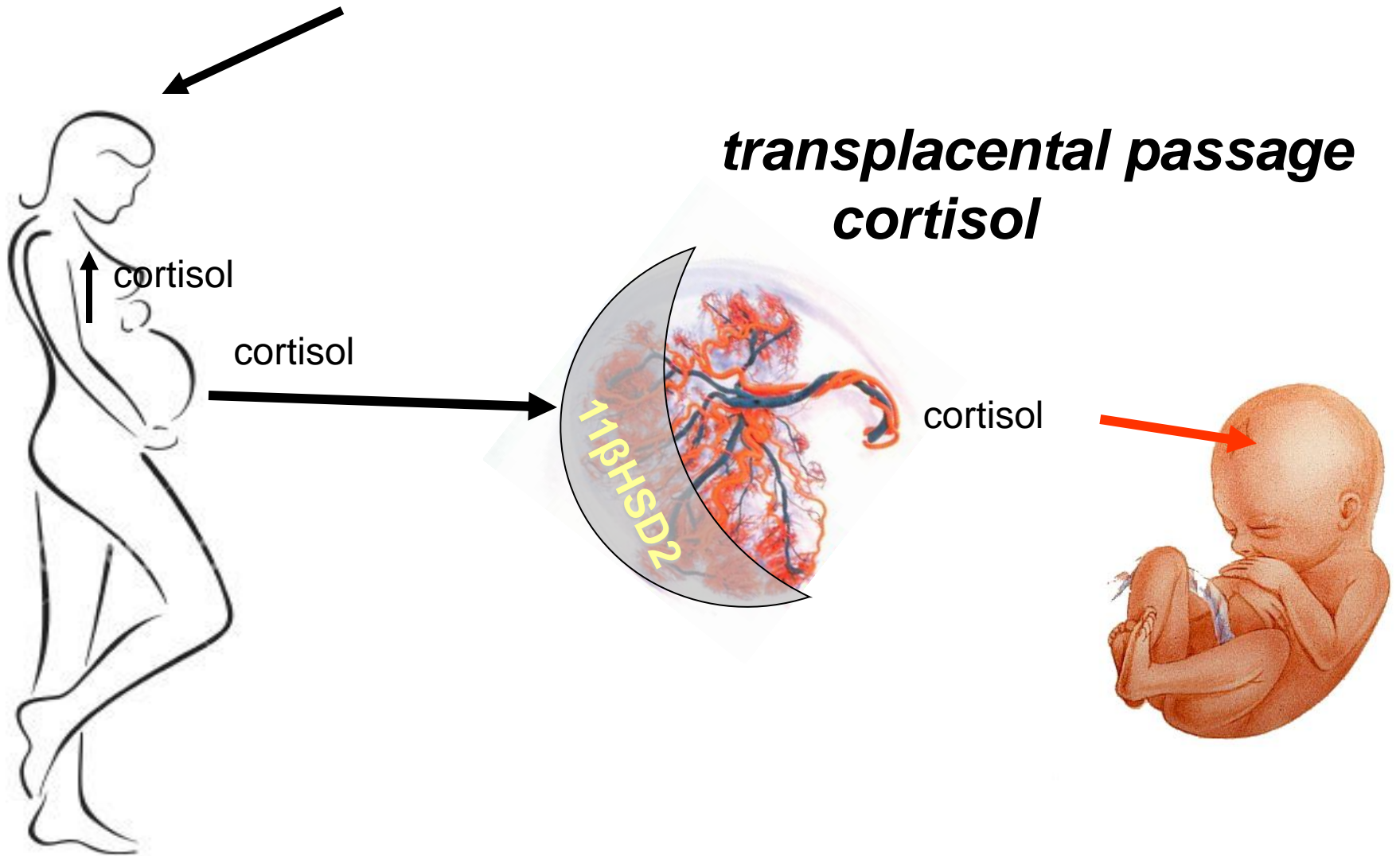
$r = -0.339$, $r^2 = 0.115$, $p = 0.007^{**}$, $N = 62$



Mechanisms : Serotonin overexposure



Maternal stress/anxiety/mental illness



Bayley Scales of Infant Development (BSID-II)



**Study child's
cognitive
(MDI)
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at
17 months**



Ainsworth's 'Strange Situation' Assessment

1. Parent and child are alone in a room.



2. Child explores the room without parental participation.



3. Stranger enters the room, talks to the parent, and approaches the child.



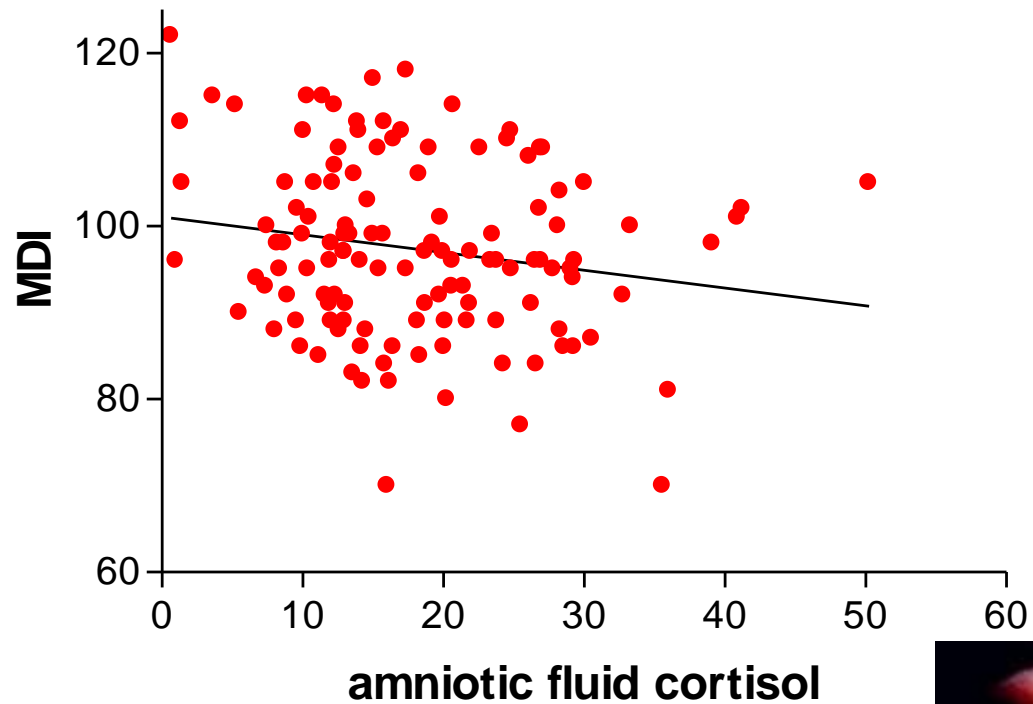
4. Parent quietly leaves the room.



5. Parent then returns and comforts the child.

Correlation between amniotic fluid cortisol and cognitive development

$r = -0.245$ $n = 125$ $p = 0.006$

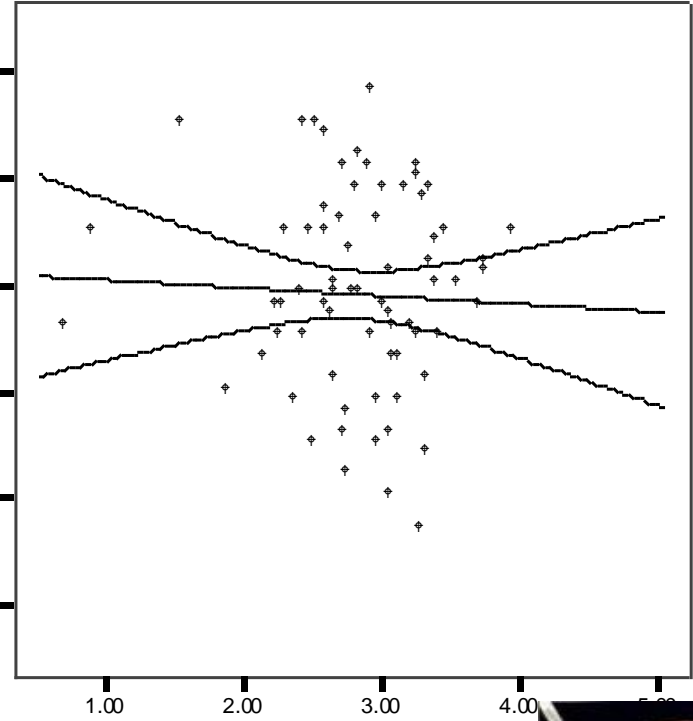
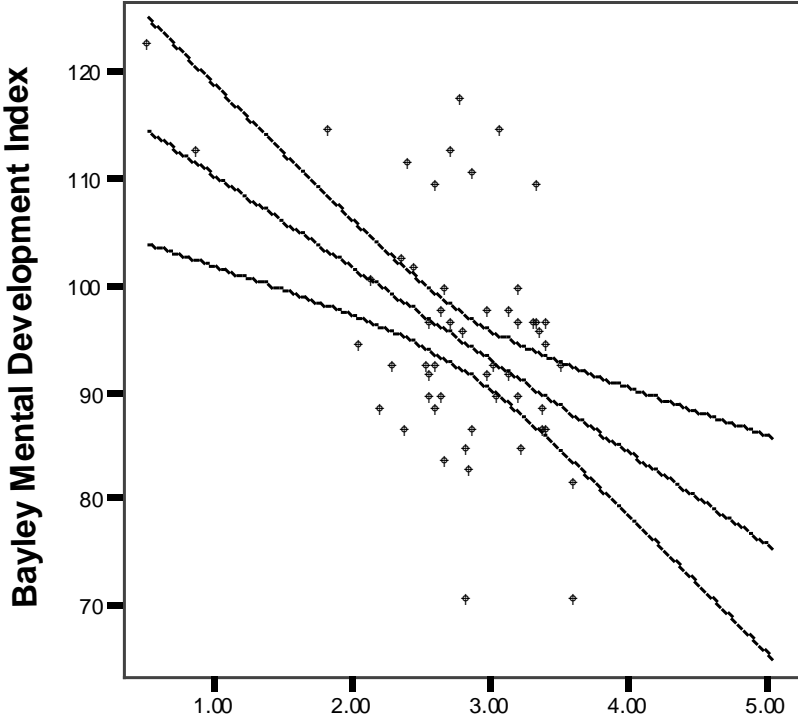


Effect of Maternal Attachment on association between AF cortisol and Cognitive Development



Insecure

Secure



Ln AF cortisol



- Higher in utero exposure to cortisol is associated with lower cognitive function
- Sensitive early mothering can reverse the effects of high in utero exposure to cortisol

But insensitive mothering can increase fearfulness in the child

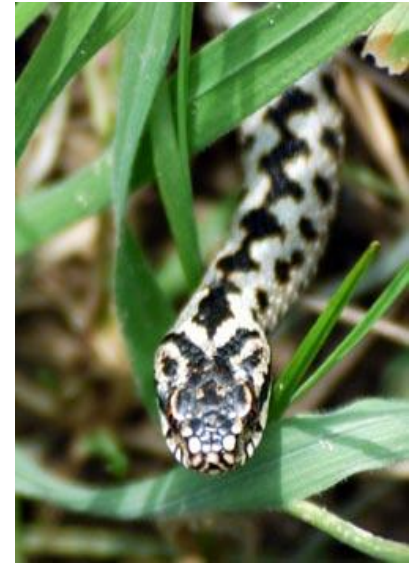


Early mothering is just as important as what happens in the womb for child outcome.

Why?

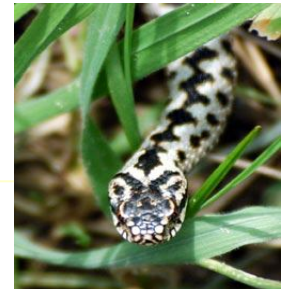
Predictive adaptive value of changes due to prenatal stress in a stressful environment in the wild?

- Anxiety/fear reactivity- beneficial effects of more vigilance
- ADHD- shifting attention helps if predators about



Evolutionary benefit of changes caused by prenatal stress

- Anxious more vigilant
- ADHD readily shifted attention
- Impulsive more willing to explore new environments
- Conduct disorder more willing to break rules
- Aggressive fight predators or other tribes
- Cognitive deficit side effect of ADHD or
- Asberger's understands things in a different way



Other findings explained by evolutionary perspective

Sex differences

- females stay to look after offspring- more anxiety/vigilance
- males explore and fight, more conduct disorder, aggression, ADHD

Effects of stress across the range

- dose response effect to respond to the degree of stress in the environment

Children not all affected in the same way

- genetic variation basis for natural selection

Public health implications of reducing stress/anxiety/depression in pregnancy

- More than one million children in UK suffer from neurodevelopmental disorders
- Attributable load of neurodevelopmental problems due to prenatal stress 10-15%
- Potential to reduce number of affected children in the UK by 100,000-150,000

Interventions?

- Different for each mother
- Detect and treat anxiety and depression in pregnancy
- Help with relationship problems
- Social support
- Practical help with housing etc
- Help to teach sensitive mothering -video feedback?





www.beginbeforebirth.org

