Sex-Differences in Child and Adolescent Psychopathology: A Test of Evolutionary Hypotheses

Jonathan Hill and the Wirral Child Health and Development Team
Helen Sharp, Andrew Pickles, John Quinn, Chris Murgatroyd, Nicky Wright, Elizabeth Braithwaite

The Scope of Evolutionary Hypotheses

- Selection of adaptive traits
- Selection of psychopathology?
- Selection of adaptive traits in the human social environment of 300,000 years or more –how much do we know about that?
- Selection at individual or population level, e.g. selected vulnerability of male foetuses?
- Selection of adaptive traits based on ‘best bets’, e.g. foetal selection of traits fitted for the anticipated environment

What should Evolutionary Perspectives for Psychiatry Achieve?

That they help to explain major puzzles in the field

That they lead us to generate hypotheses and conduct data analyses, which we would not have thought of without them

That the effects which we identify as a result are large enough to make a difference

That the findings can be replicated

That the ‘surprisingness’ of the research leads to surprising clinical or public health conclusions

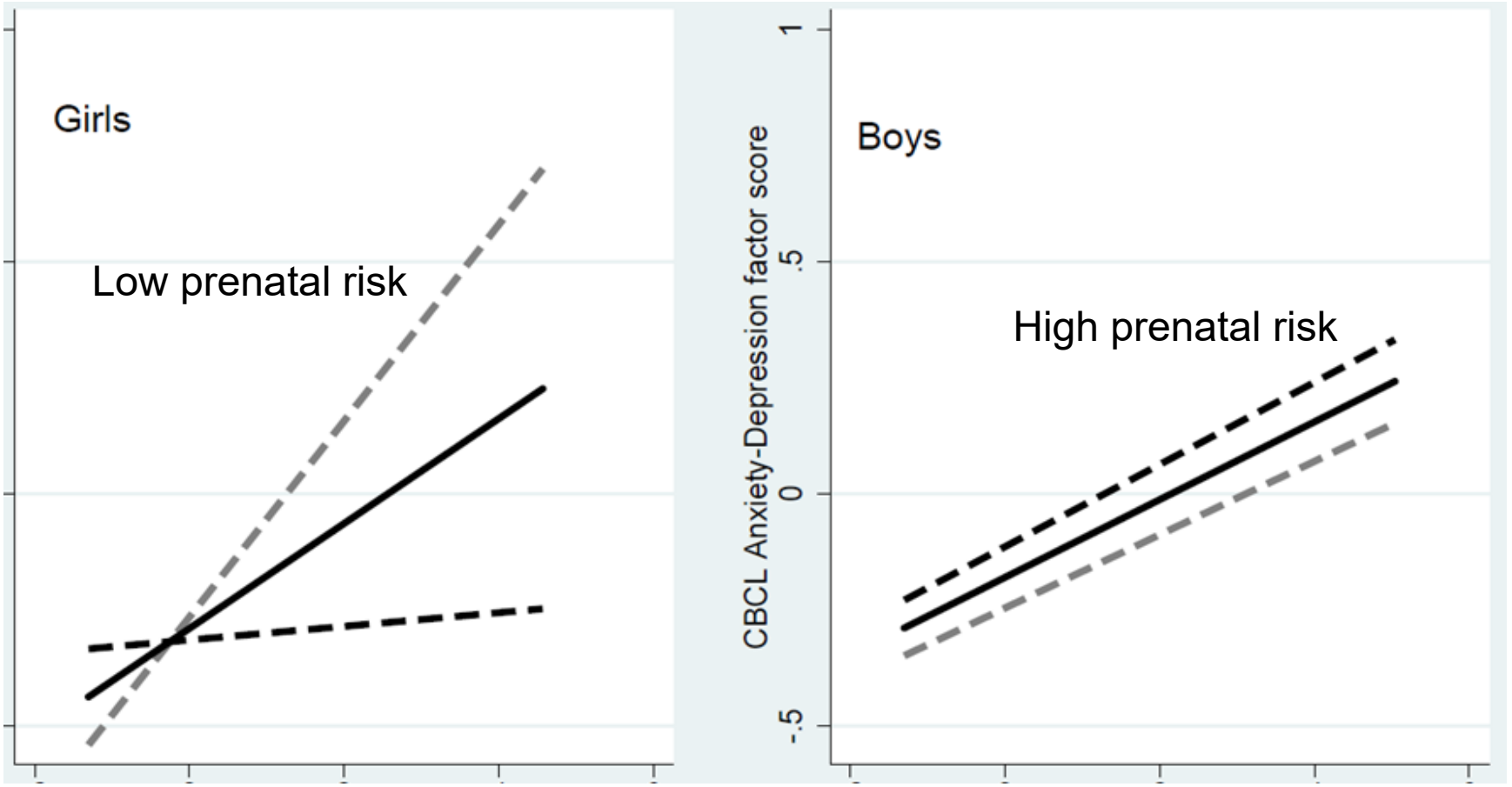
Two Evolutionary Hypotheses

Trivers-Willard hypothesis - male births favoured when maternal condition is good, females when poor - vulnerable male, adaptive female.

Predictive Adaptive Response – foetal adaptations anticipate later environmental conditions – favourable outcomes where there is prenatal-postnatal continuity

If the protective effect in females arises from foetal anticipation of matched environments (PAR hypothesis), mismatches between maternal conditions during pregnancy and the postnatal environment will create vulnerability specifically in females

Prenatal – postnatal Interplay



Natural Selection of Parental Ability to Vary the Sex Ratio of Offspring

Robert L. Trivers and Dan E. Willard

Science (1973) **179** (4068), 90-92.

Theory and data suggest that a male in good condition at the end of the period of parental investment is expected to outreproduce a sister in similar condition, while she is expected to outreproduce him if both are in poor condition.

Accordingly, natural selection should favor parental ability to adjust the sex ratio of offspring produced according to parental ability to invest.

Data from mammals support the model: As maternal condition declines, the adult female tends to produce a lower ratio of males to females.

J Physiol 592.11 (2014) pp 2357–2368 2357

SYMPOSIUM-RELATED

The biology of developmental plasticity and the Predictive Adaptive Response hypothesis

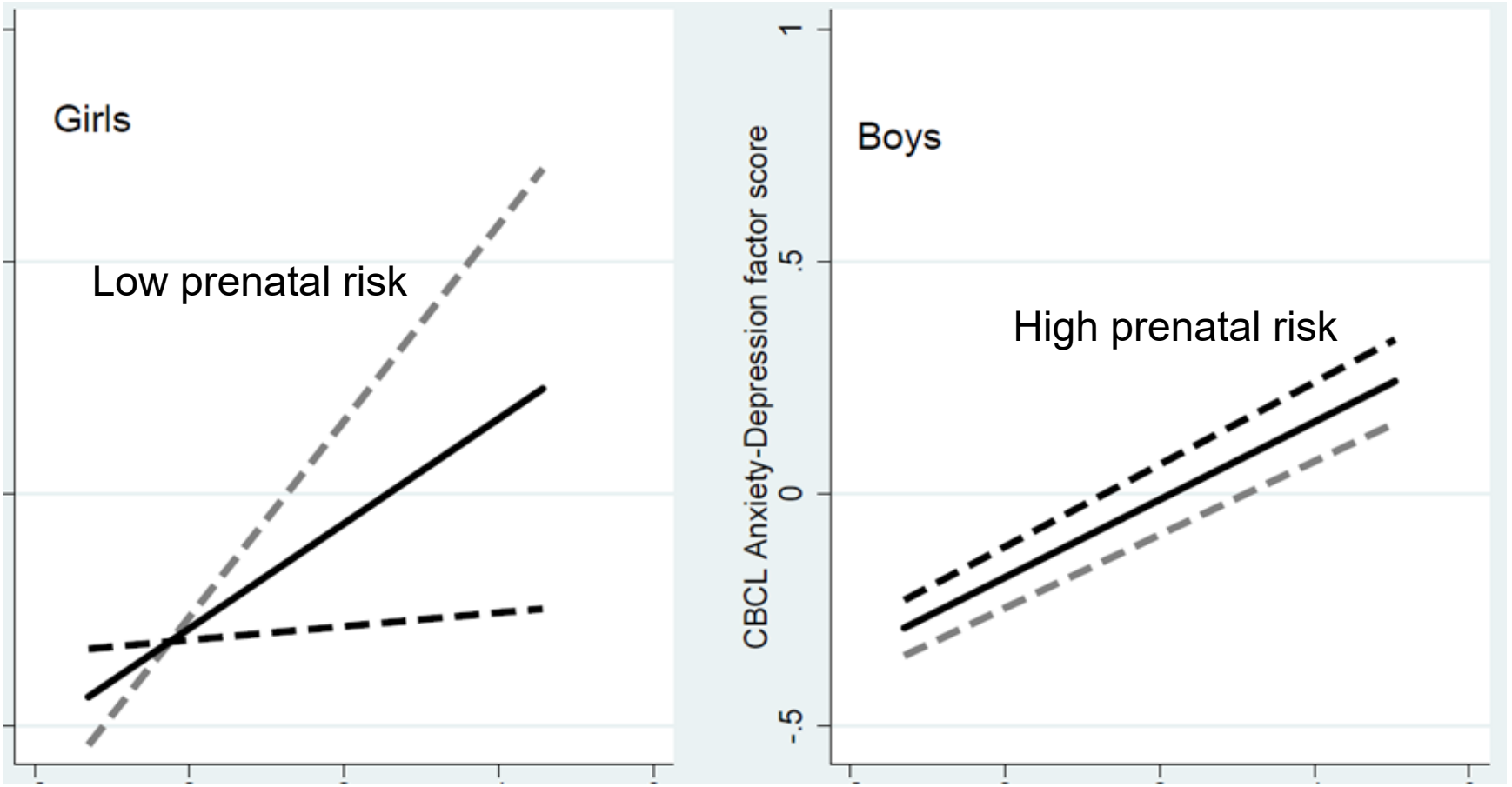
Patrick Bateson[1], Peter Gluckman[2] and Mark Hanson[3]

The Predictive Adaptive Response (PAR) hypothesis refers to a form of developmental plasticity in which cues received in early life influence the development of a phenotype that is normally adapted to the environmental conditions of later life.

When the predicted and actual environments differ, the mismatch between the individual's phenotype and the conditions in which it finds itself can have adverse consequences for Darwinian fitness and, later, for health.

Many of the mechanisms underlying developmental plasticity involve molecular epigenetic processes, and their elucidation in the context of PARs and more widely has implications for the revision of classical evolutionary theory.

Prenatal – postnatal Interplay



The Possible role of Glucocorticoid Mechanisms – Starlings!

Female

Prenatal Low	Postnatal Low
Prenatal High	Postnatal High

Male

Prenatal Low	Postnatal Low
Prenatal High	Postnatal High

Love, O. P., & Williams, T. D. (2008). The adaptive value of stress-induced phenotypes: effects of maternally derived corticosterone on sex-biased investment, cost of reproduction, and maternal fitness. *The American Naturalist*, *172*(4), E135

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Prenatal sham injection coupled with maternal wing clipping leads to elevated corticosterone reactivity in female chicks only

Prenatal injection of corticosterone reduces live male births, and alters sex ratio in favour of females

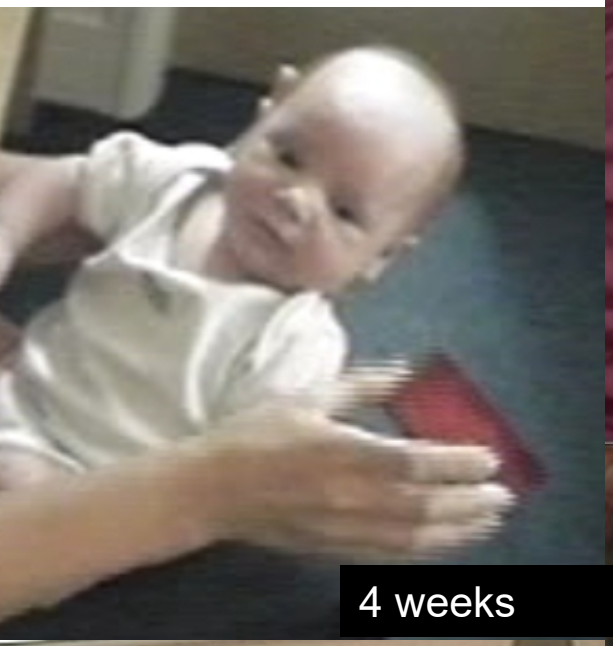
What is the Major Puzzle in the Field?

Rutter, M., Caspi, A., & Moffitt, T. E. (2003). Using sex differences in psychopathology to study causal mechanisms: unifying issues and research strategies. *Journal of child psychology and psychiatry*, *44*(8), 1092-1115.

Males more than females, early onset (except schizophrenia), externalizing, neuro-cognitive, persistent non-episodic

Females more than males, onset after puberty, internalizing, affective, episodic

Wirral Child health and Development Study UK


4 weeks

6 months

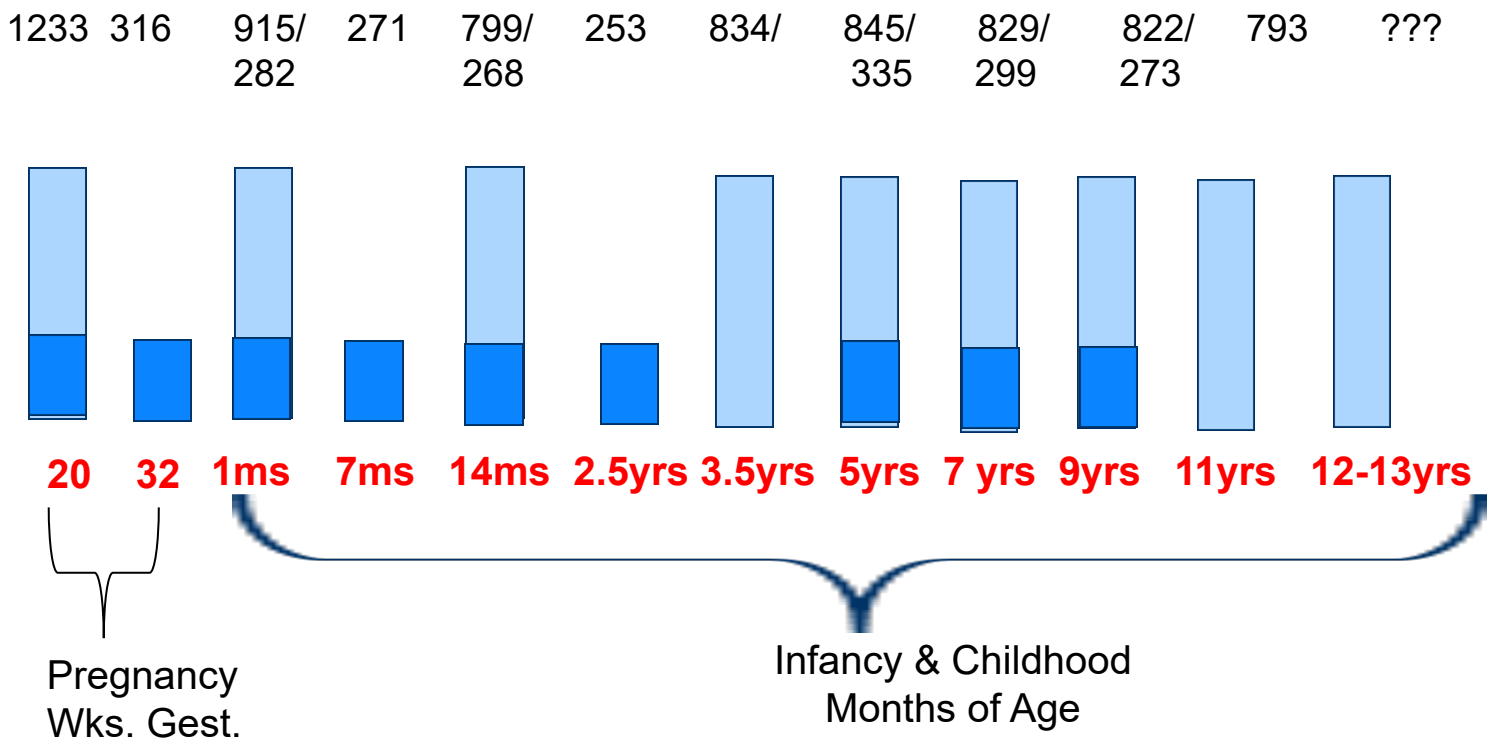

14 months


2.5 years


3.5 years


4.5 years

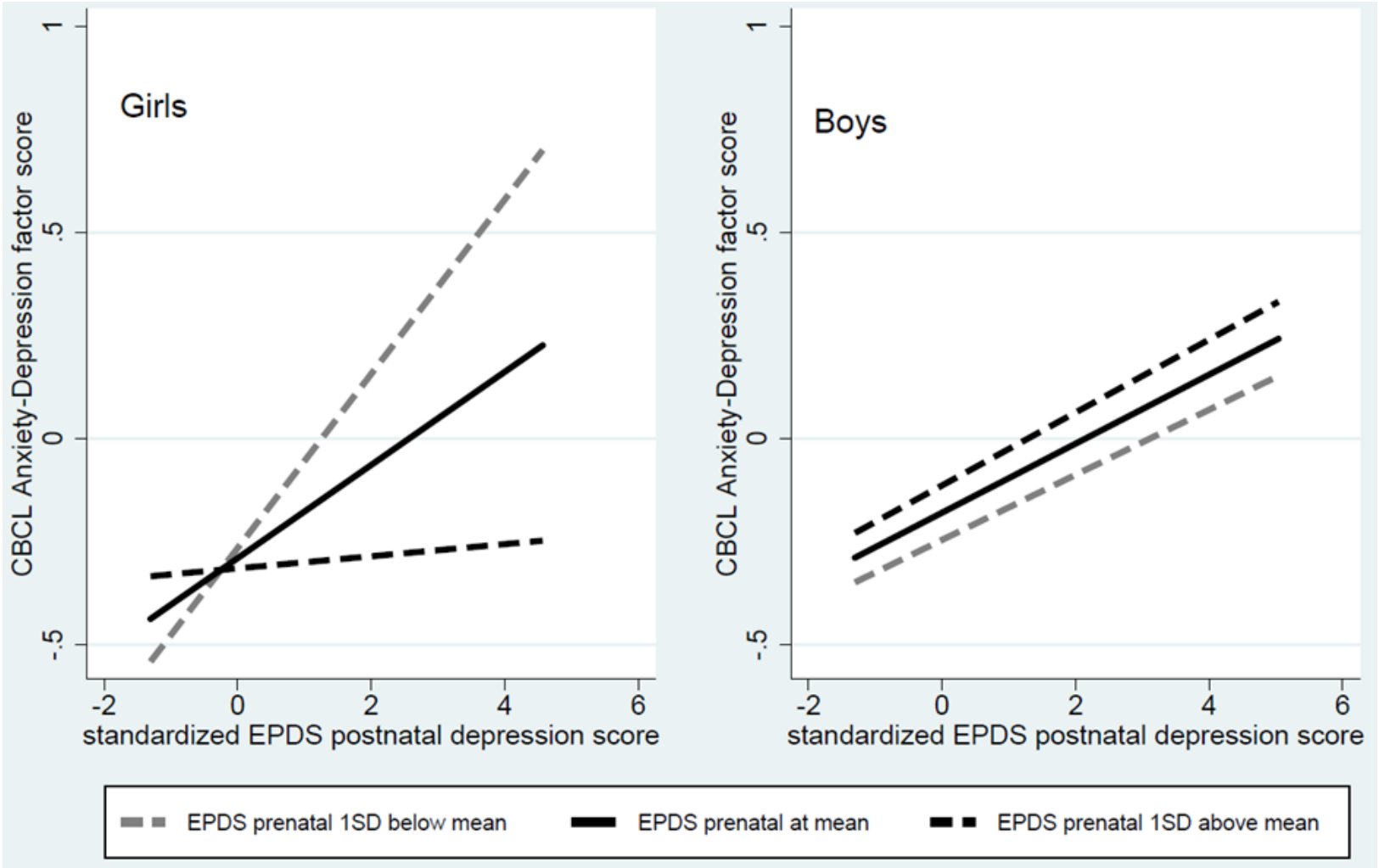
Wirral Child Health & Development Study - Numbers



Sample details in Sharp et al (2012) PLOS One 10 (7) e45446

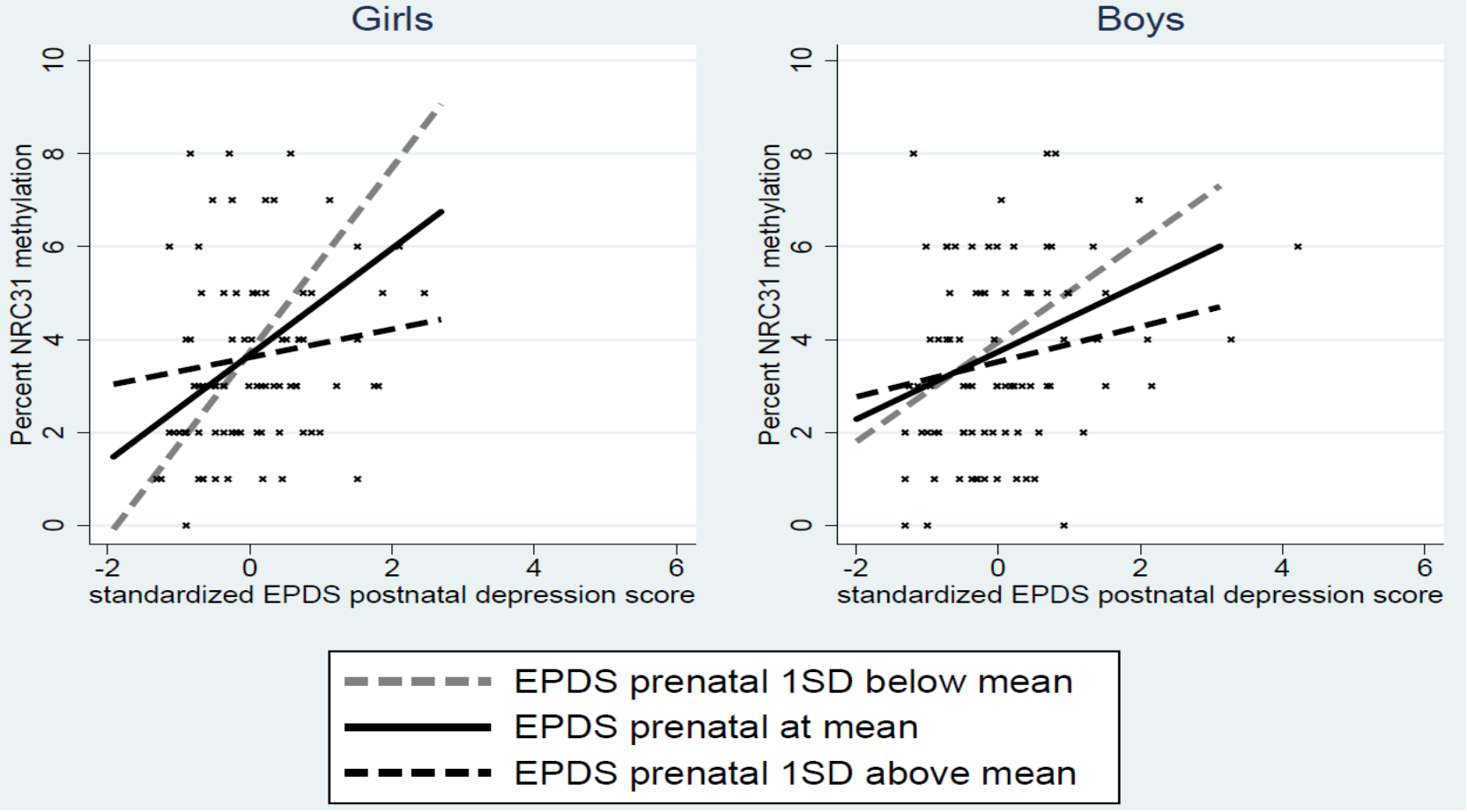
Pre- and Postnatal Maternal Depression, Child anxiety-depression 2.5 – 5.0 yrs

Hill et al (2019). Mismatched prenatal and postnatal maternal depressive symptoms and child behaviours: a sex-dependent role for NR3C1 DNA methylation in the Wirral Child Health and Development Study. *Cells*, *8*(9), 943.

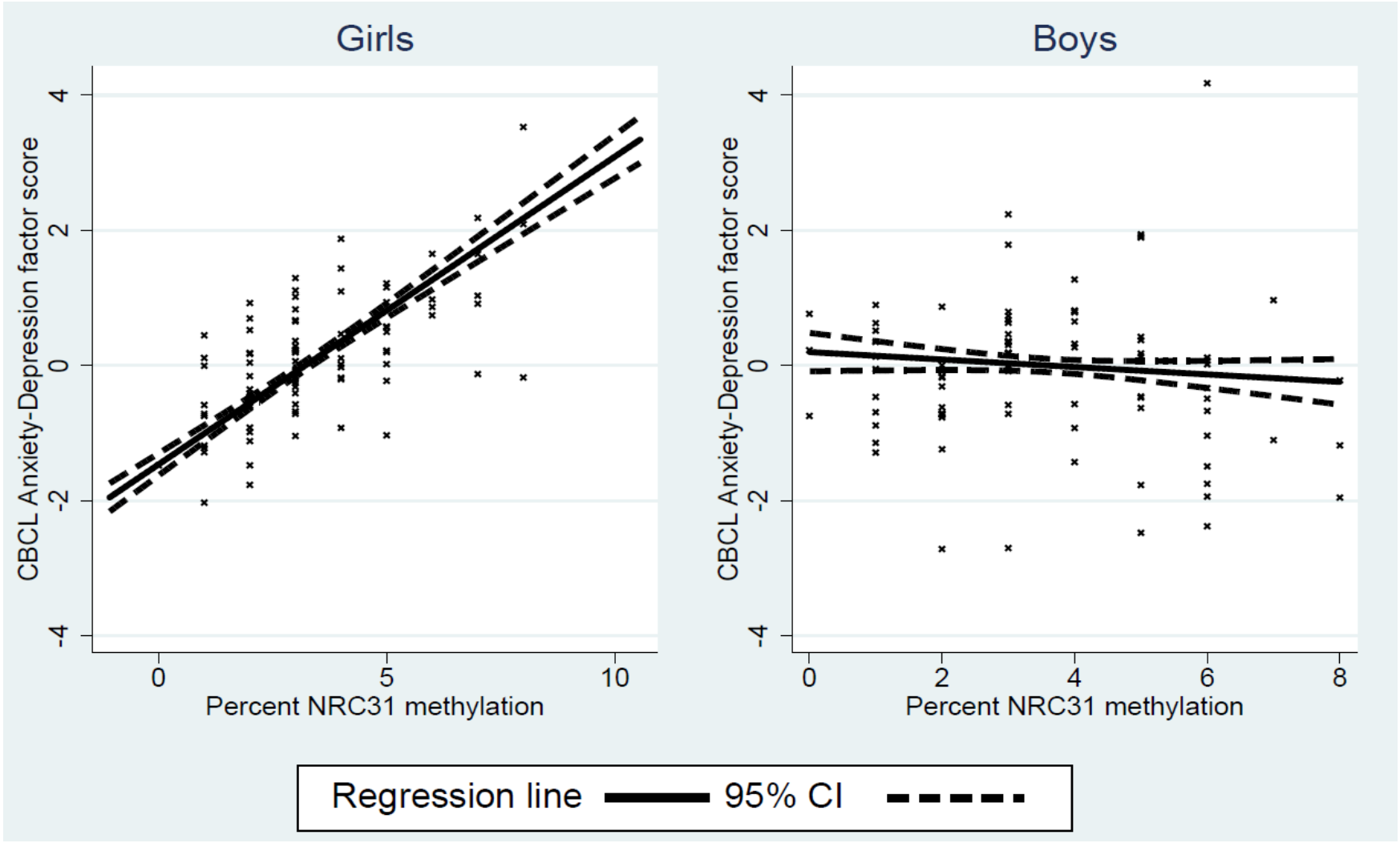


Pre- and Postnatal Maternal Depression, NR3C1 (GR) Methylation, 14 Mnths

Murgatroyd et al 2015). Effects of prenatal and postnatal depression, and maternal stroking, at the glucocorticoid receptor gene. *Translational psychiatry*, *5*(5), e560-e560.

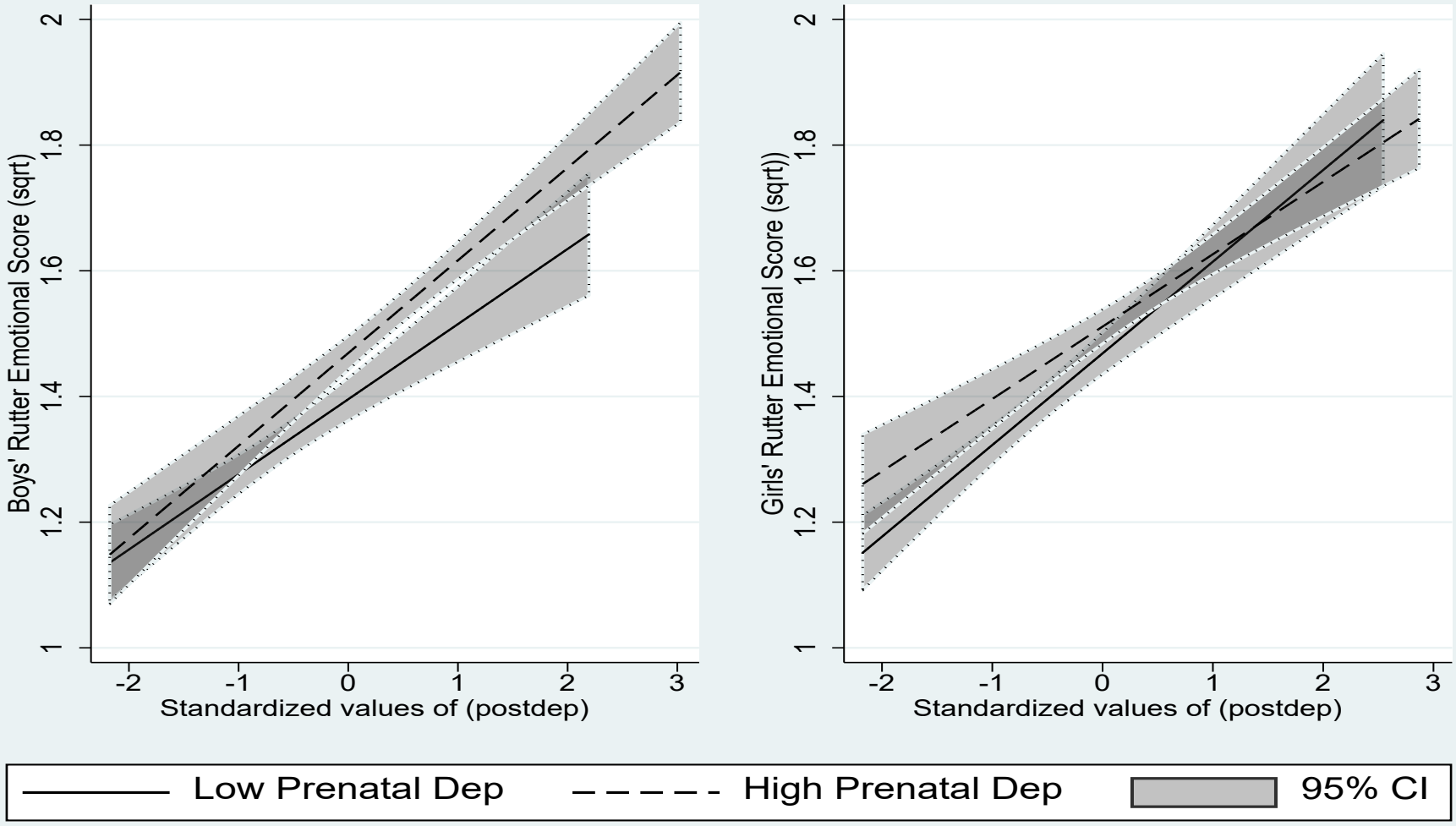


NR3C1 (GR) Methylation, 14 Mnths, Child anxiety-depression 2.5 – 5.0 yrs



Replication in ALSPAC?

Braithwaite et al (2020). Sex differences in foetal origins of child emotional symptoms: a test of evolutionary hypotheses in a large, general population cohort. *Journal of Child Psychology and Psychiatry*, *61*(11), 1194-1202.



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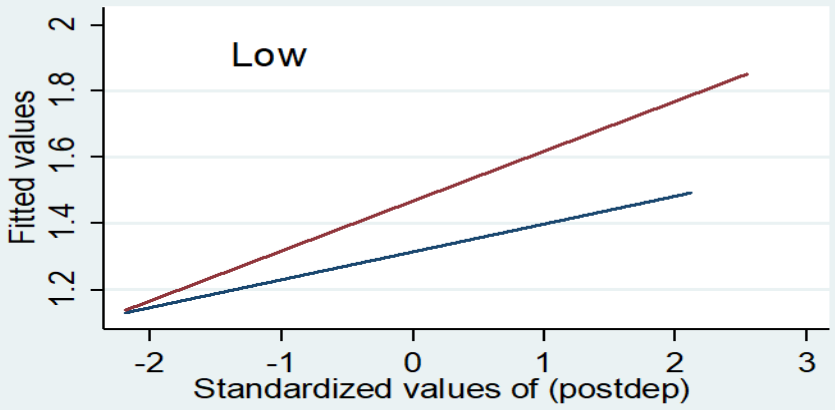
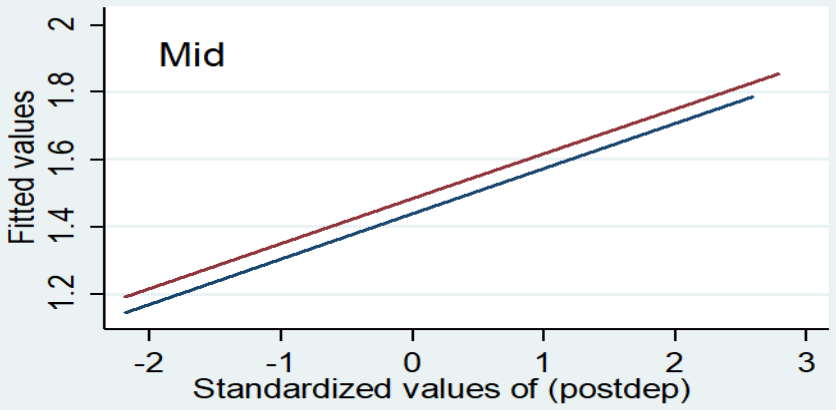
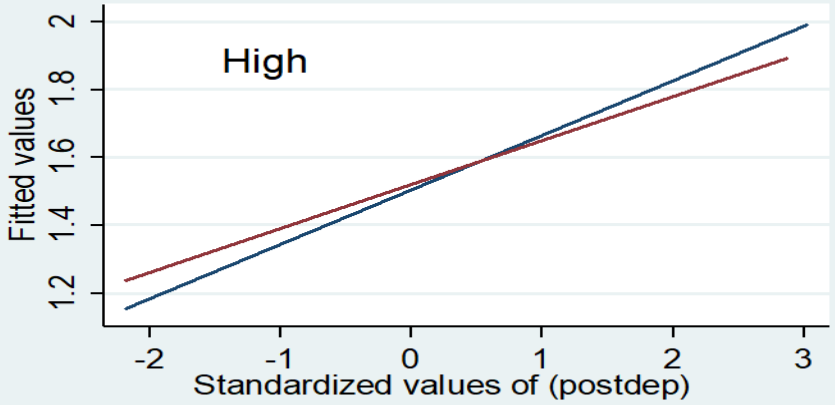
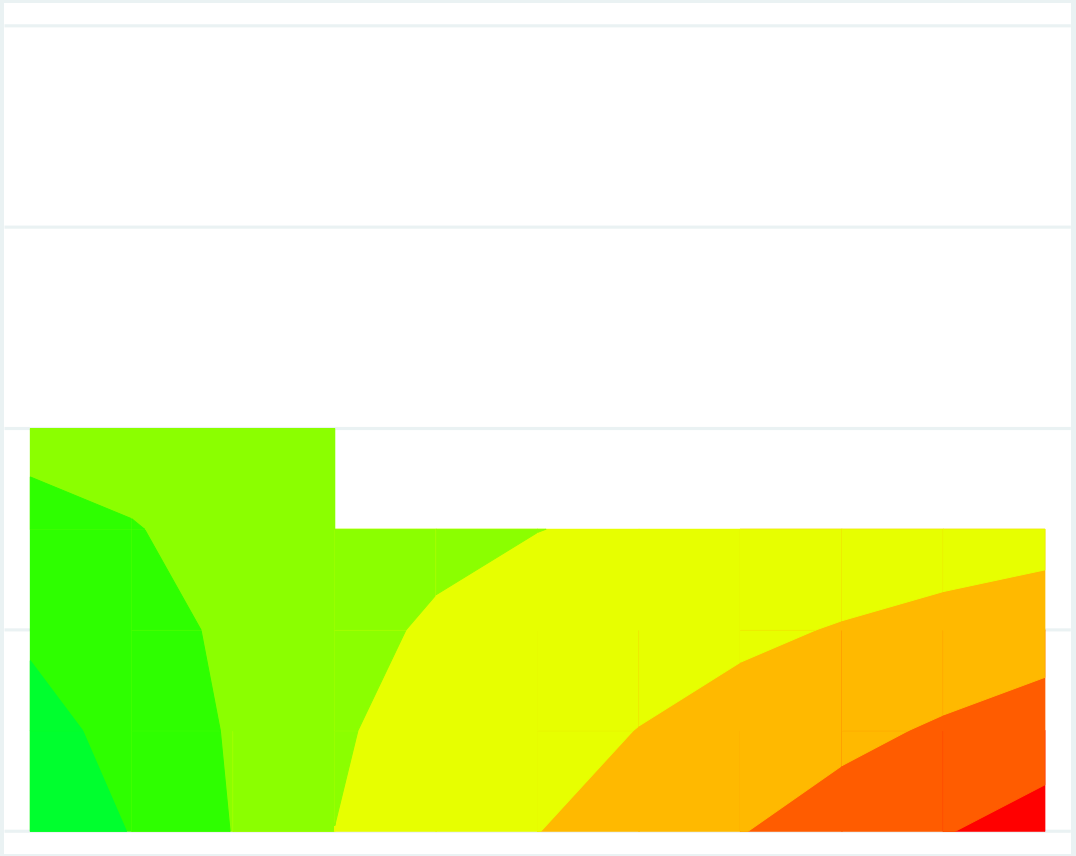




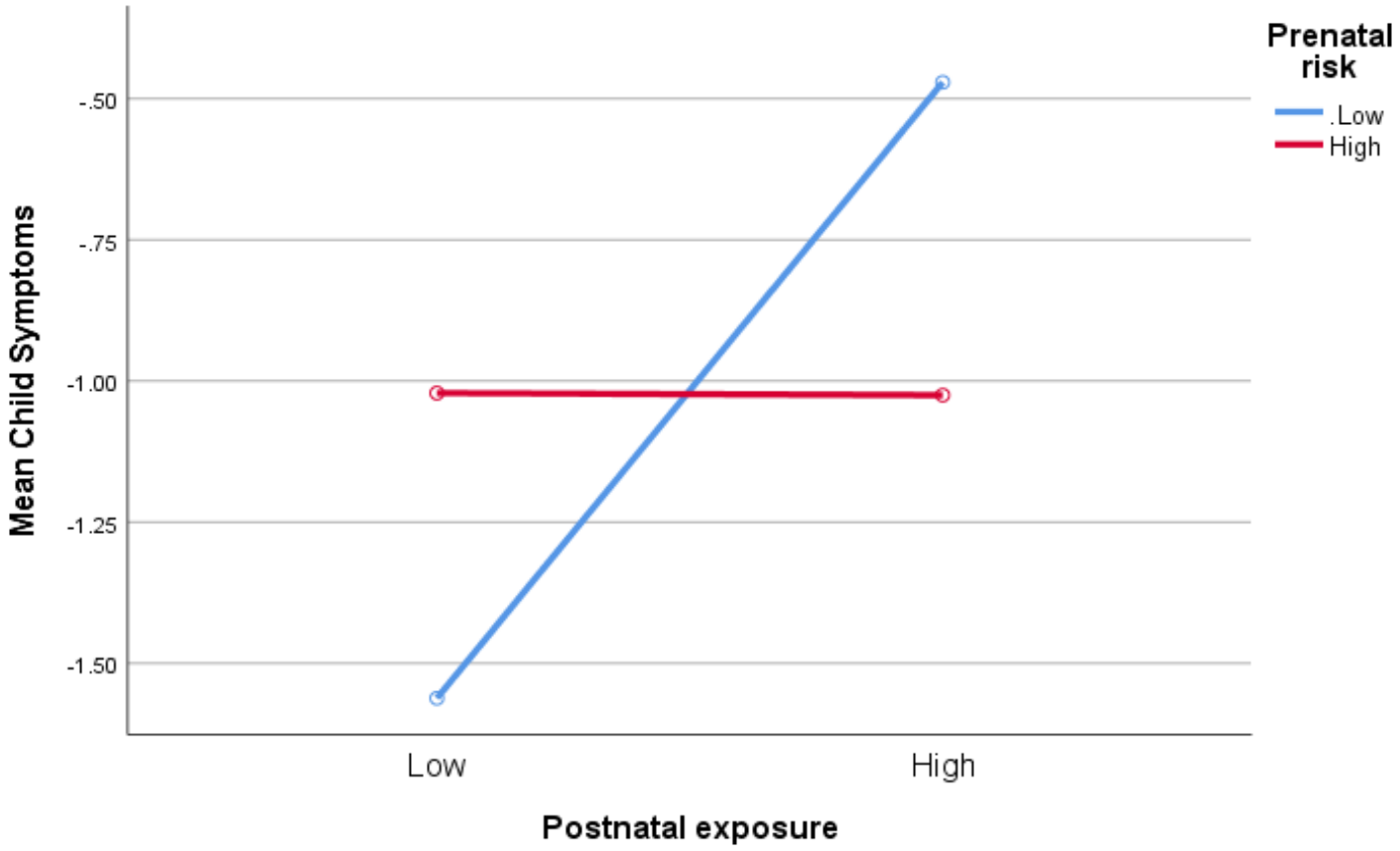


Boys Girls

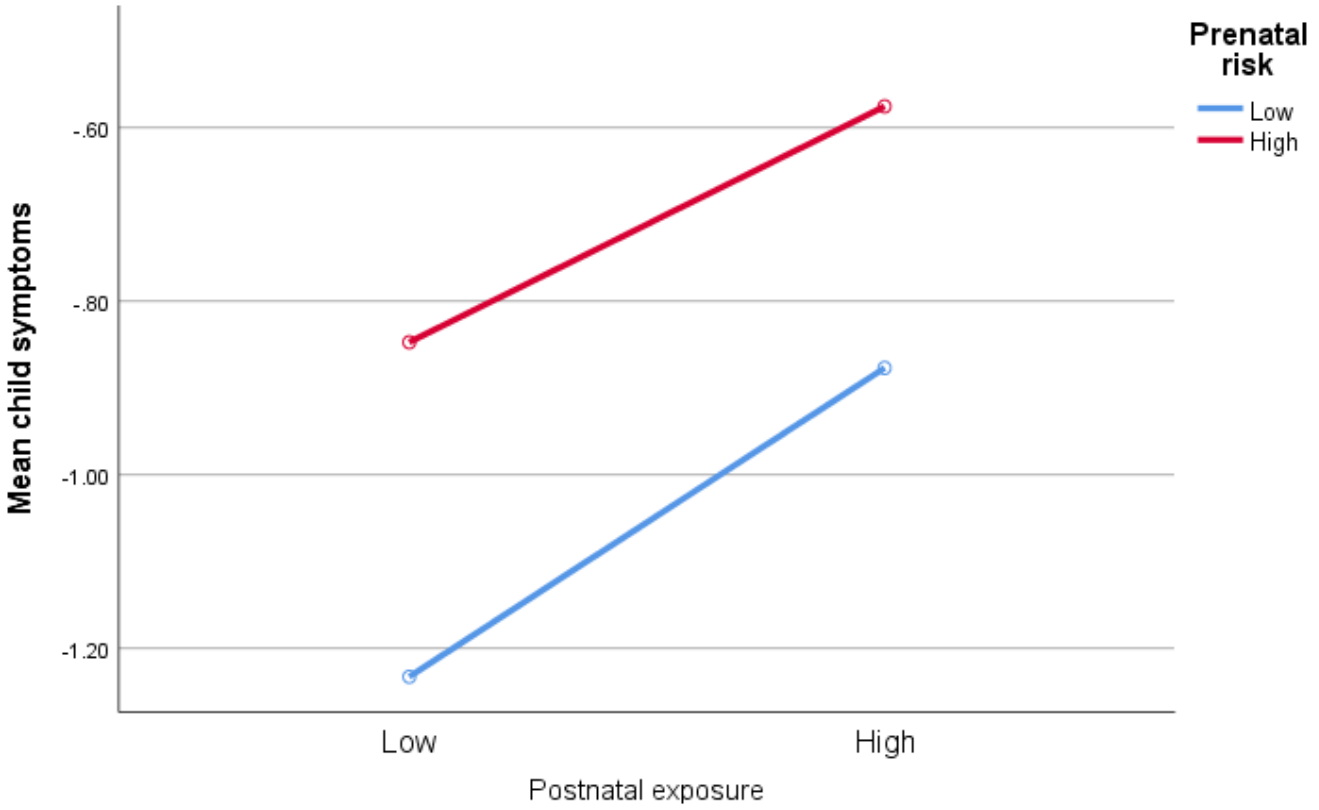
Contours of Male and Female Depression



Was Partner Violence in the Social Environment of past 300,000 years? Prenatal Anxiety, Partner Violence - Girls



Prenatal Anxiety, Postnatal Exposure to Partner Violence - Boys



What should Evolutionary Perspectives for Psychiatry Achieve?

That they try to explain major puzzles in the field – YES SEX DIFFERENCES IN RISK AND MECHANISM FOR PSYCHOPATHOLOGY

That they lead us to generate hypotheses and conduct data analyses, which we would not have thought of without them - YES

That the effects which we identify as a result are large enough to make a difference – POSSIBLY

That the findings can be replicated – THE JURY IS OUT

That the 'surprisingness' of the research leads to surprising clinical or public health conclusions – COULD DO!

Vagal Reactivity in the Still Face at 7 Months

Tibu et al (2014)
Development and Psychopathology

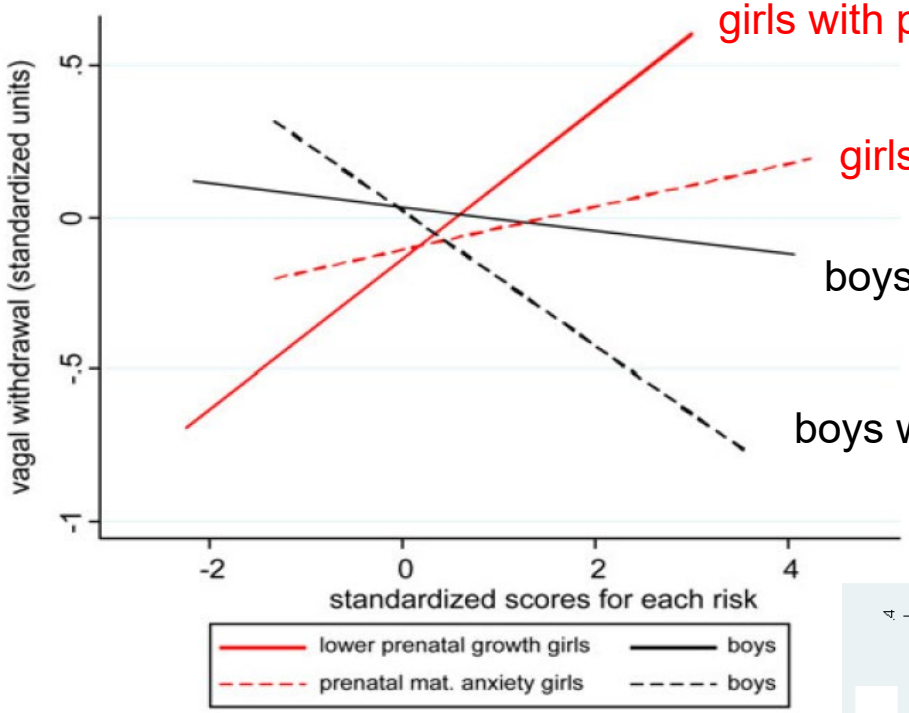
Evidence for sex differences in fetal programming of physiological stress reactivity in infancy

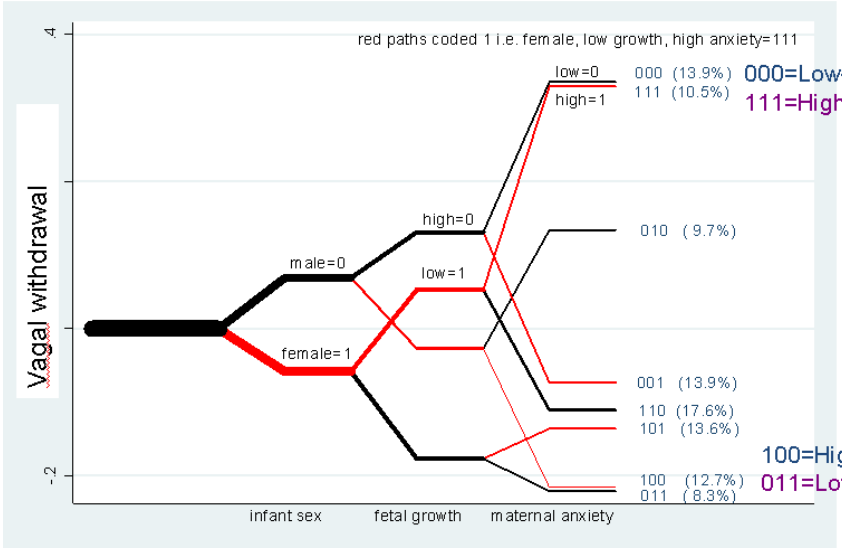
girls with poorer prenatal growth

girls with mums with prenatal anxiety

boys with poorer prenatal growth

boys with mums with prenatal anxiety





What might the signs of the adaptive female after birth? Risk or resilience?

- Lower birthweight
- Elevated HPA axis or other physiological reactivity?
- Elevated arousal?
- Higher amygdala reactivity?
- Higher emotionality?

And males?

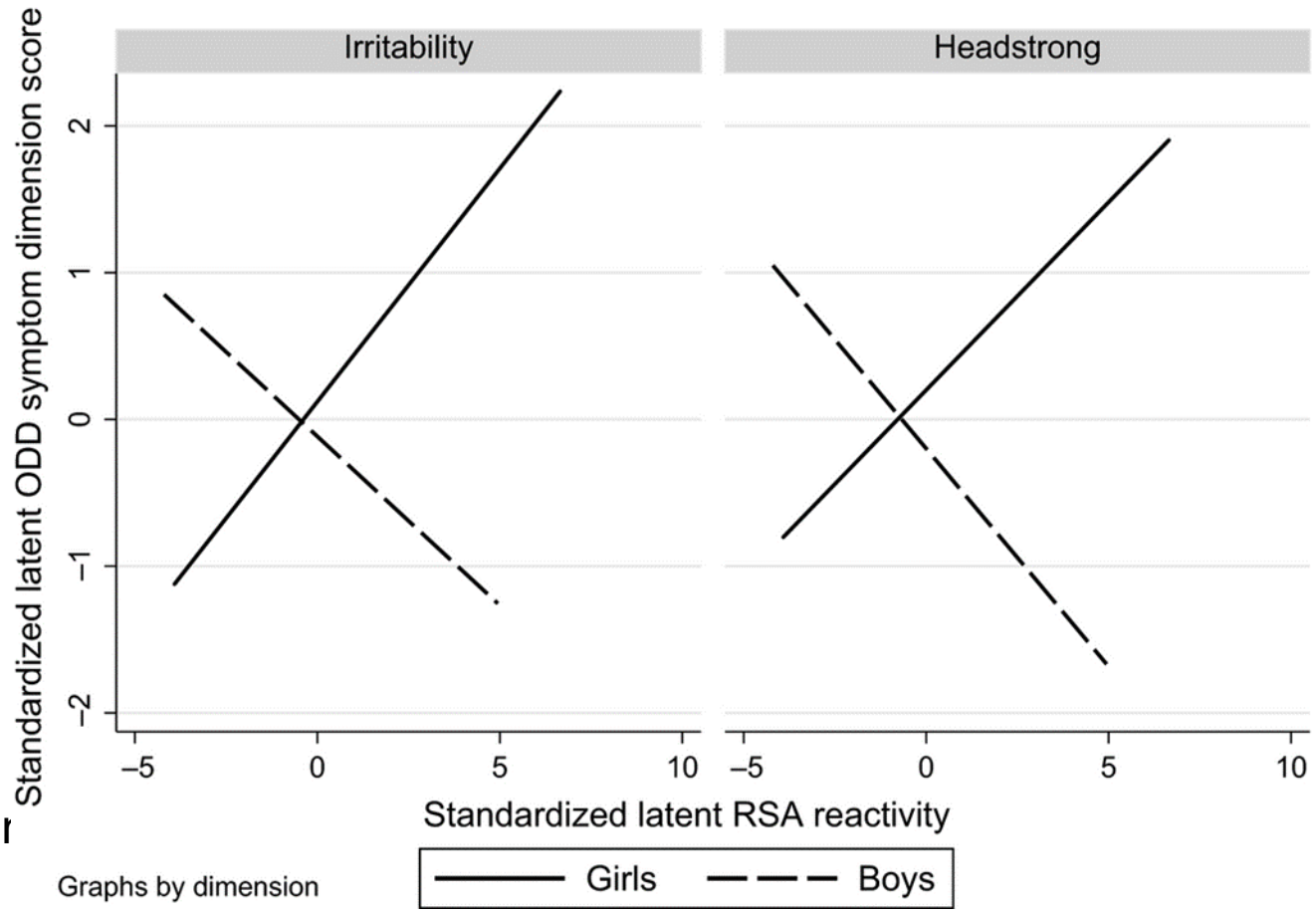
- Do they lack these effects or are they in the opposite direction?
- Elevated evidence of vulnerability such as motor, cognitive or attentional deficits?

Consequences of altered early physiological reactivity

The Journal of Child Psychology and Psychiatry
Journal of Child Psychology and Psychiatry 58:9 (2017), pp 988–997 doi:10.1111/jcpp.12750

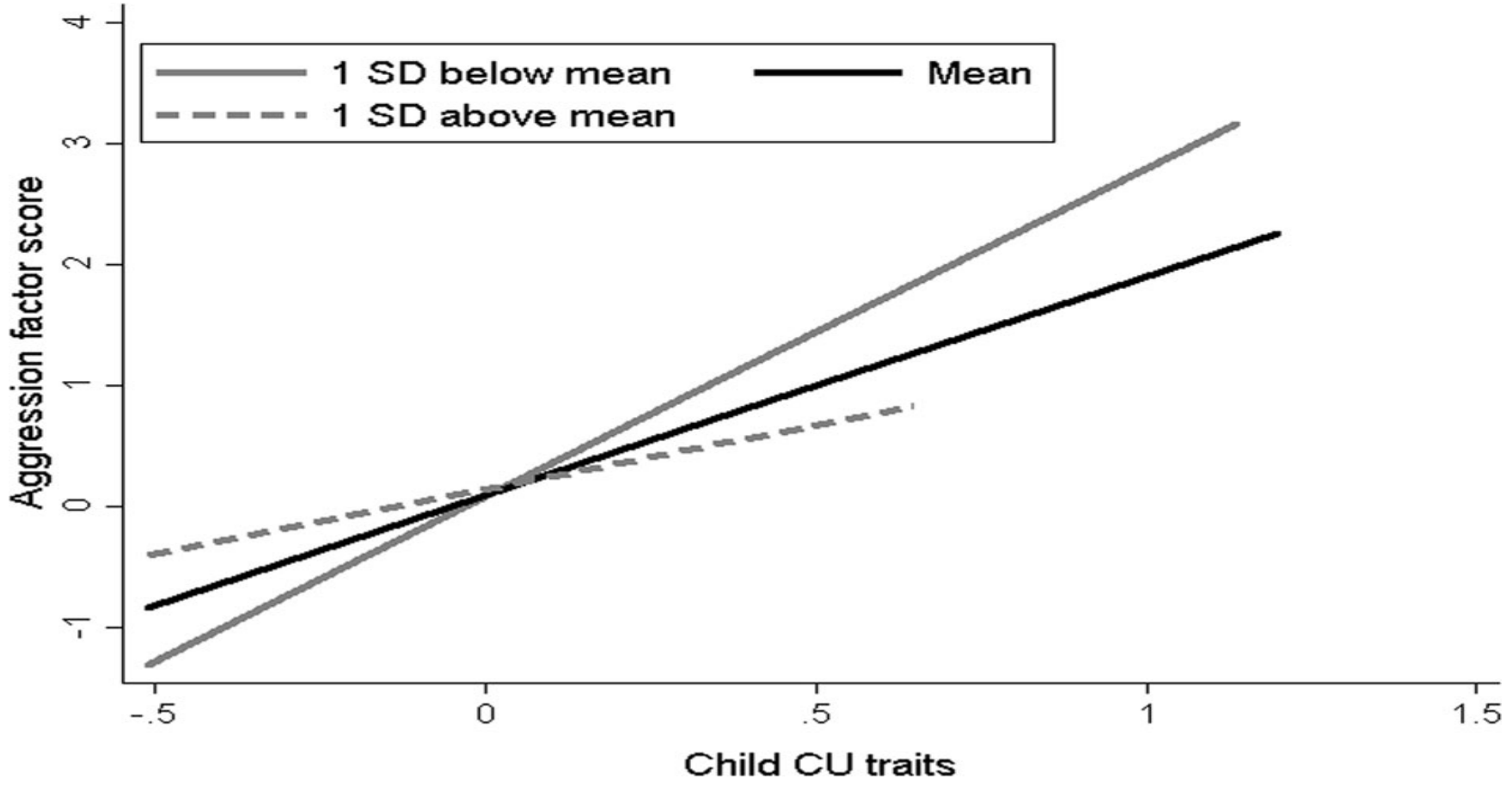
Sex differences in the associations between vagal reactivity and oppositional defiant disorder symptoms

Pablo Vidal-Ribas,[1] Andrew Pickles,[2] Florin Tibu,[3] Helen Sharp,[4] and Jonathan Hill[5]



Wright et al. (2019)
Translational Psychiatry

Callous-unemotional traits, low cortisol reactivity and physical aggression in boys: findings from the Wirral Child Health and Development Study



REPRODUCTION REVIEW

Sex differences in developmental programming models

Catherine E Aiken[1,2] and Susan E Ozanne[2]

[1]Department of Obstetrics and Gynaecology, The Rosie Hospital and NIHR Cambridge Comprehensive Biomedical Research Centre, University of Cambridge, PO Box 223, Cambridge CB2 0SW, UK and [2]Metabolic Research Laboratories, Institute of Metabolic Science, Addenbrooke's Hospital, University of Cambridge, Cambridge CB2 0QQ, UK

Correspondence should be addressed to C E Aiken at Department of Obstetrics and Gynaecology, The Rosie Hospital and NIHR Cambridge Comprehensive Biomedical Research Centre, University of Cambridge; Email: cema2@cam.ac.uk

Abstract

It is suggested that male and female development could be viewed as separate processes from the time of conception, with differences in both timing and outcomes.

Preterm males have poorer cognitive and motor outcomes than preterm females

Synthetic steroid, betamethasone improves outcomes for preterm births, more in females than males, because higher 11β-hydroxysteroid dehydrogenase-2 (11β HSD2) levels in female placentas preserves foetal cortisol reactivity and hence better cardiovascular stability in infants

Placenta 2017

Review: Placental adaptations to the presence of maternal asthma during pregnancy

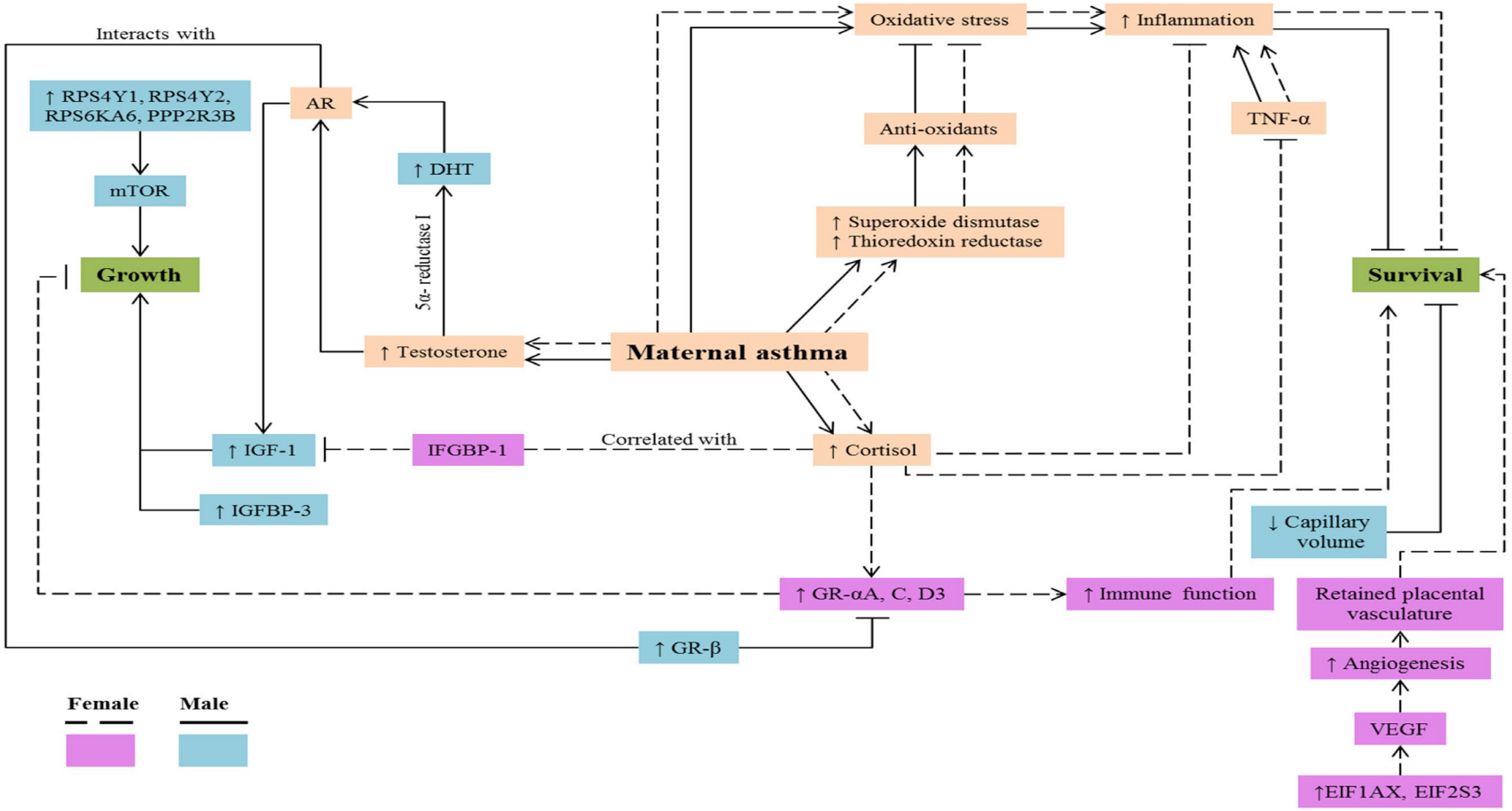
A.S. Meakin, Z. Saif, A.R. Jones, P.F. Valenzula Aviles, V.L. Clifton*
Mater Medical Research Institute, University of Queensland, Brisbane, Australia

We have identified that the placenta adapts to the presence of chronic, maternal asthma during pregnancy in a sex specific manner that may confer sex differences in fetal outcome.

Female foetuses more likely to have low birthweight or be small for gestational age.

Males more likely to deliver preterm and at higher risk of stillbirth especially as asthma worsens with increasing gestation.

These sex specific differences may be conferred by the placenta which adapts to reduce female growth but as a result increases female survival relative to males in pregnancies complicated by asthma.



Maternal asthma results in increased cortisol, testosterone, and oxidative stress. The female placenta adapts via modulation of immune function facilitated by increased expression of glucocorticoid receptor (GR)-αA, C, and D3; reduced placental blood flow but retained angiogenesis.

The male placenta is unable to regulate inflammation due to glucocorticoid receptor (GR)-β induced glucocorticoid resistance, resulting in no change in placental immune function and decreased angiogenesis, hence decreased survival in the presence of a second hit.

Braithwaite et al
Journal of Developmental Origins of Health and Disease (2018)

Associations between maternal prenatal cortisol and fetal growth are specific to infant sex: findings from the Wirral Child Health and Development Study