UNIVERSITY OF Southampton

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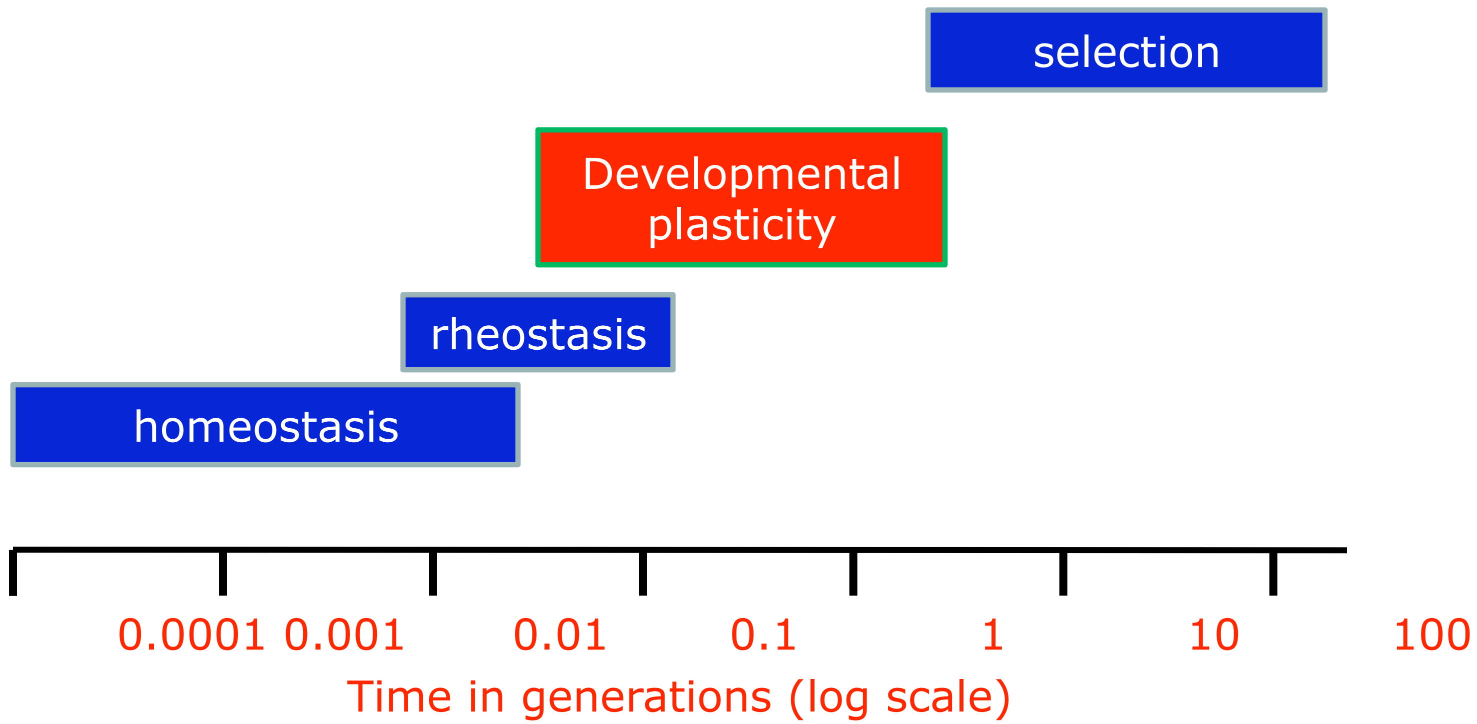
DOHaD
International Society
for Developmental
Origins of Health
and Disease

Summary

- Concepts
- Examples from animal studies – epigenetic processes
- Responses to interventions

In variable environments, organisms have several modes of adaptability to meet environmental challenges.



The importance of life course strategies

A secure developmental environment

- Investment for longevity
  - Commitment to repair
  - Commitment to tissue reserve:
  - neuronal number
  - nephron number
  - cardiomyocyte number
  - other stem cells
- Investment for large adult size
  - (Bone mass
  - Muscle growth)

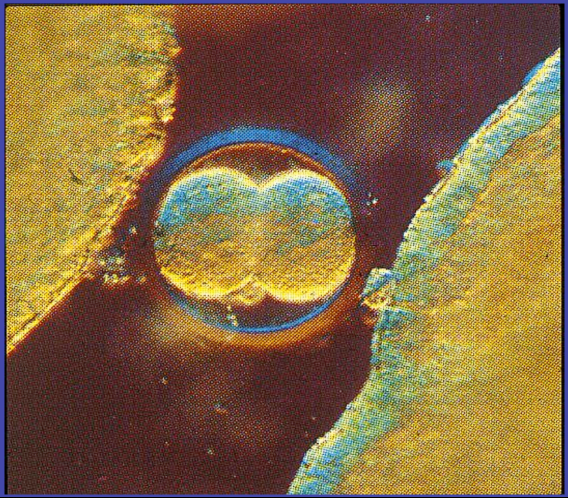
A threatening developmental environment

- Immediate trade-offs to survive
  - Smaller birth size
  - Prematurity
  - Sarcopenia
  - More fat
  - Fewer nephrons, cardiomyoctes, neurons??
- Reproductive strategy
  - early puberty
- Investment to resist environmental challenges
  - Altered HPA
  - Altered behaviour
  - Appetite & food preference

From Gluckman et al, Am J Hum Biol 2007; 19: 1-19

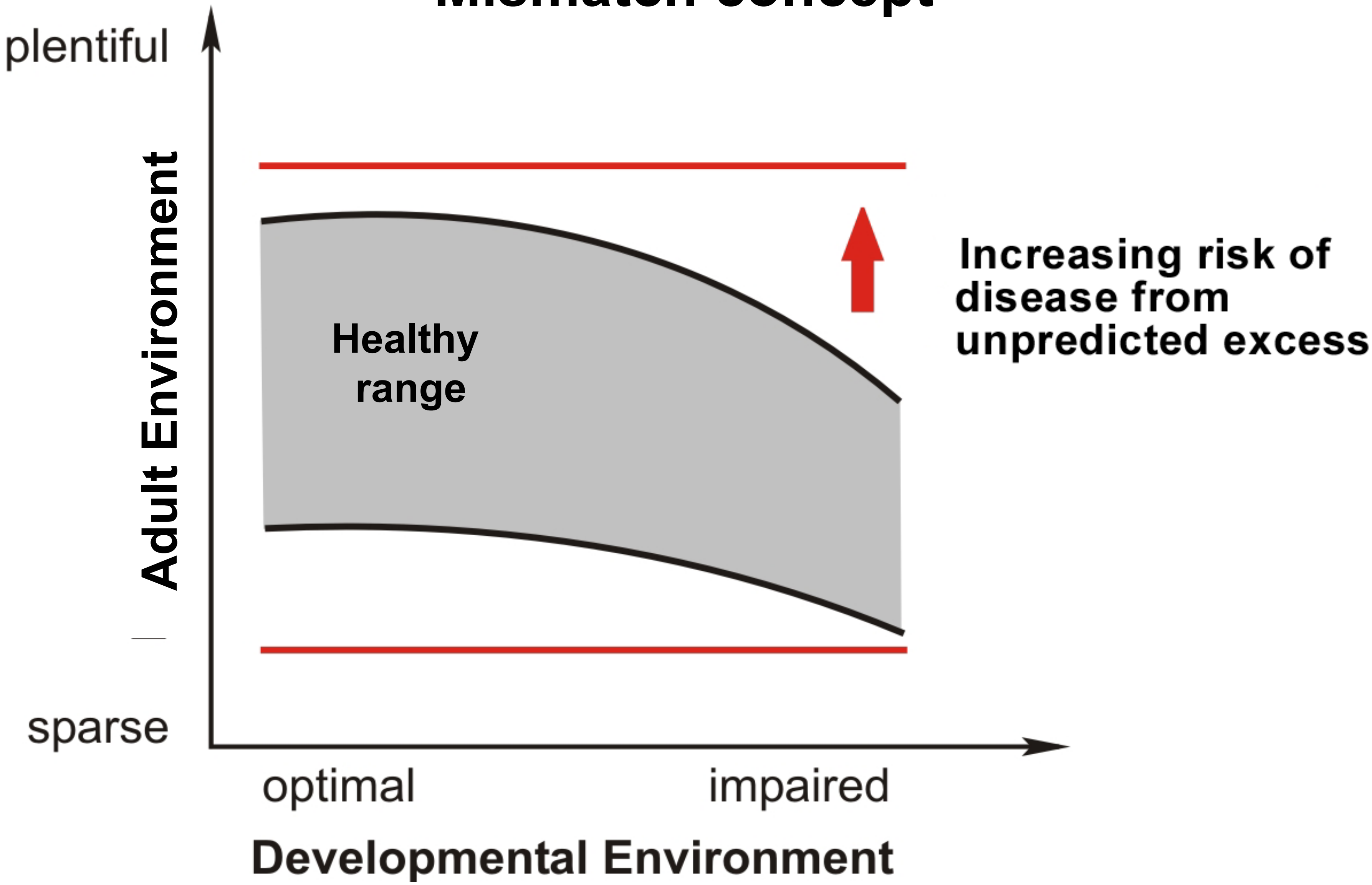
• The mother's body influences her child's development from the moment of conception

• Her body composition, diet and lifestyle teach her baby about the world in which she lives. Will his world be the same??

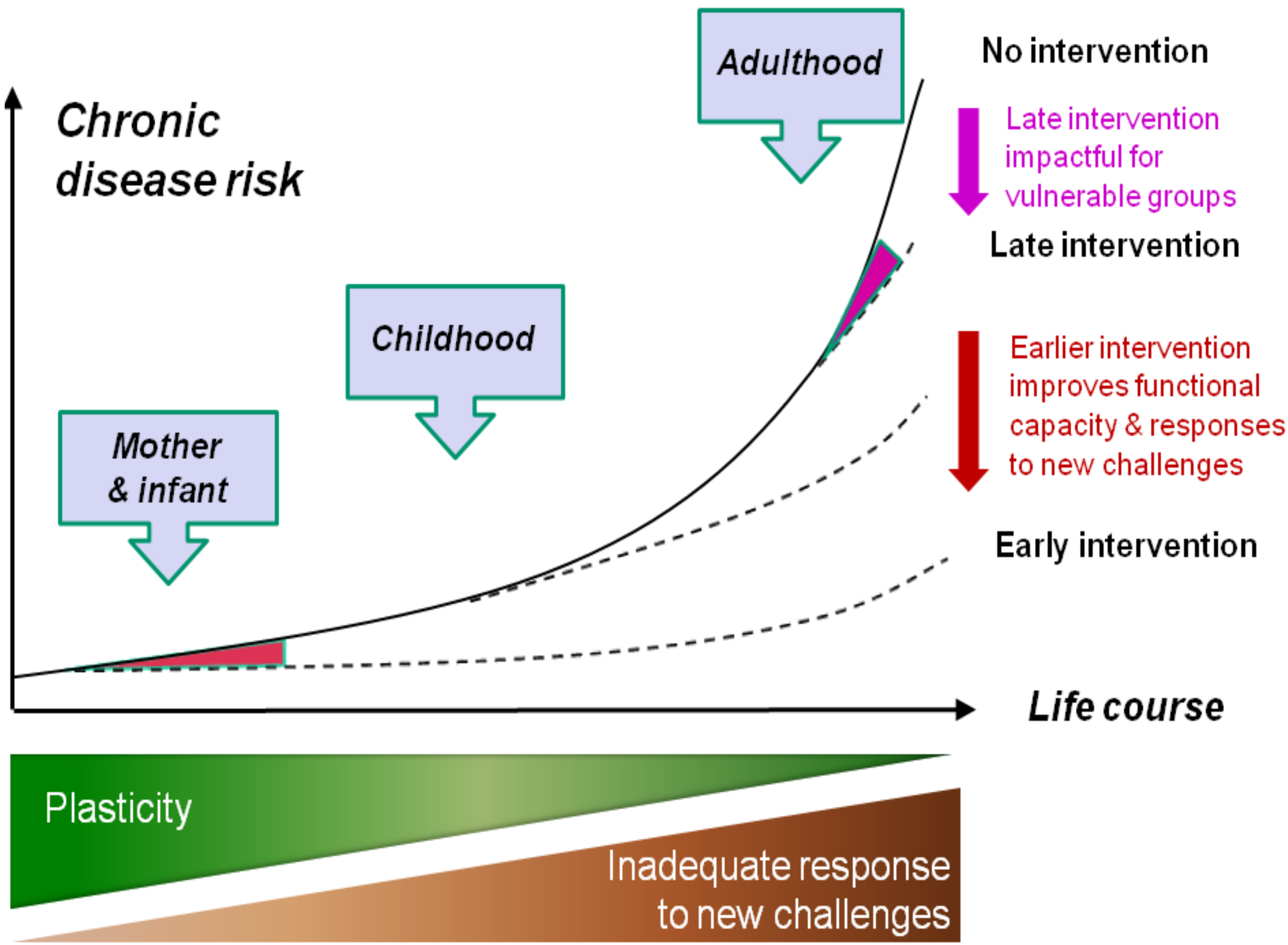


This influences her child's risk of disease for the rest of life. But what happens if the child's world turns out to be different?

Mismatch concept



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


Chronic disease risk
Mother & infant
Childhood
Adulthood
No intervention
Late intervention impactful for vulnerable groups
Late intervention
Earlier intervention improves functional capacity & responses to new challenges
Early intervention
Life course
Plasticity
Inadequate response to new challenges

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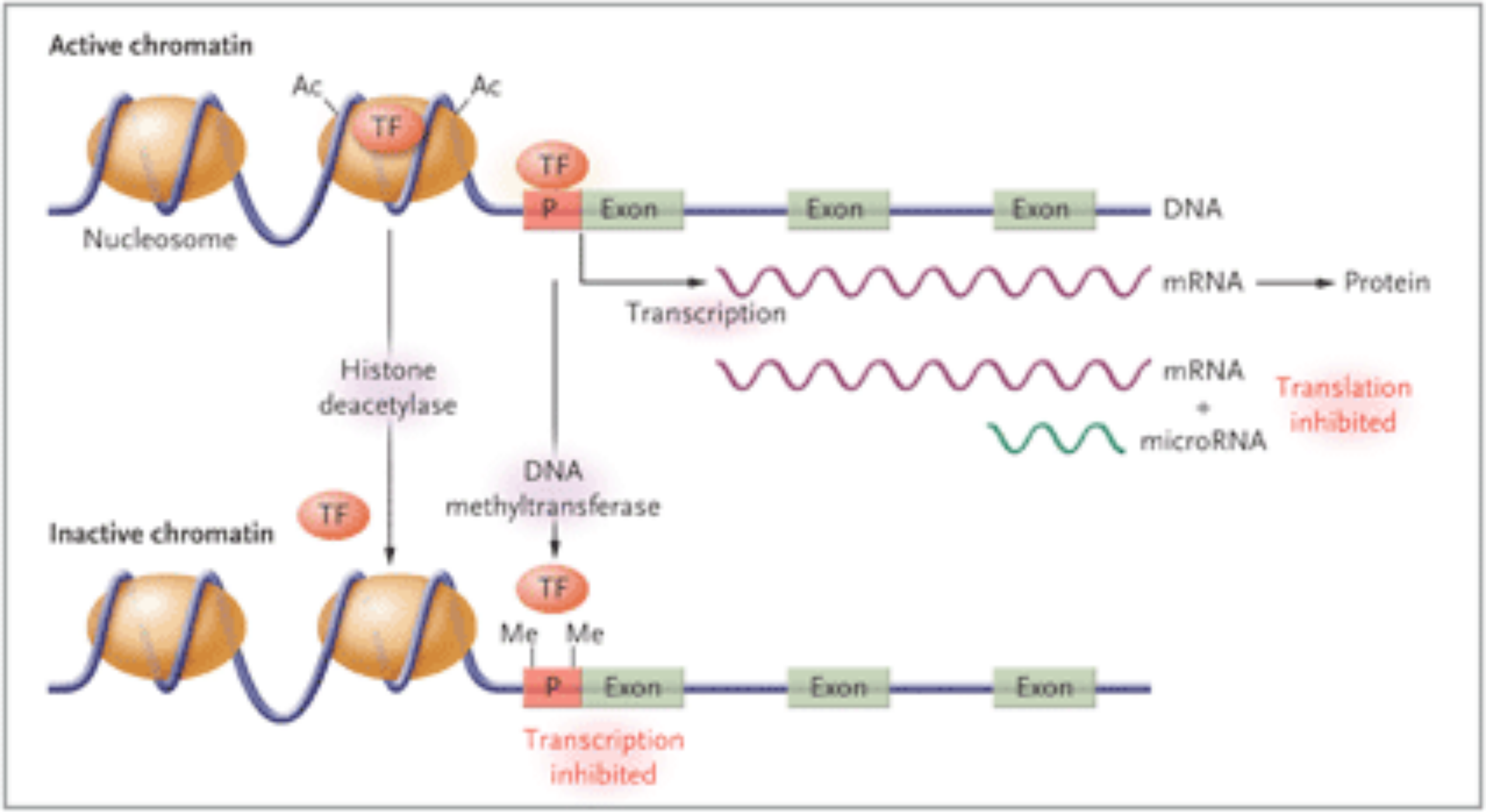
Animal models

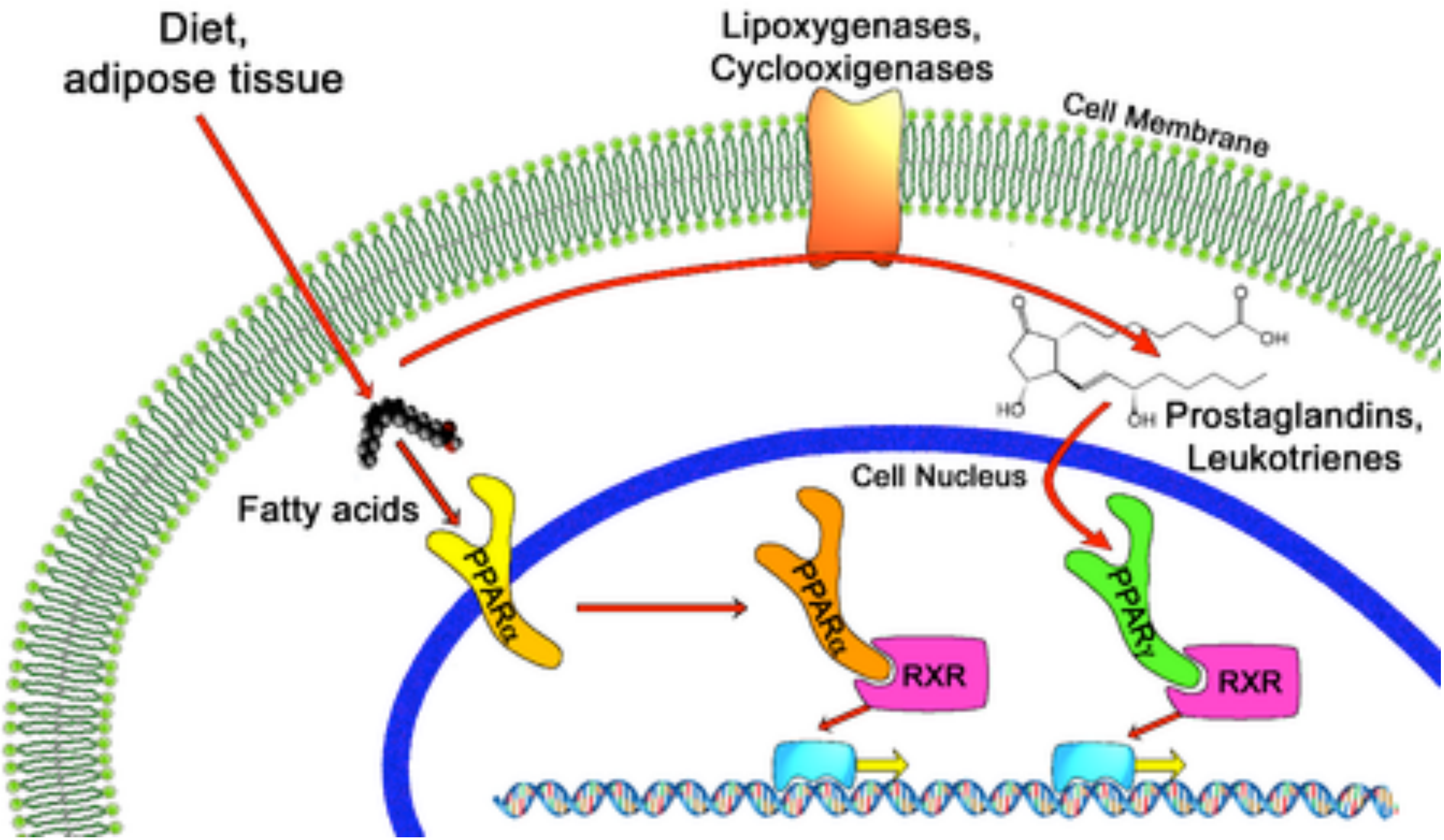
Rodents – mother fed an unbalanced diet (protein/ carbohydrate/ fat) during pregnancy, and offspring fed an adequate or excessive diet ("mismatched") This produces a range of health problems in adulthood, similar to human disease

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

Gluckman, Hanson et al New Engl J Med 2008;359:61-73.



Candidate genes

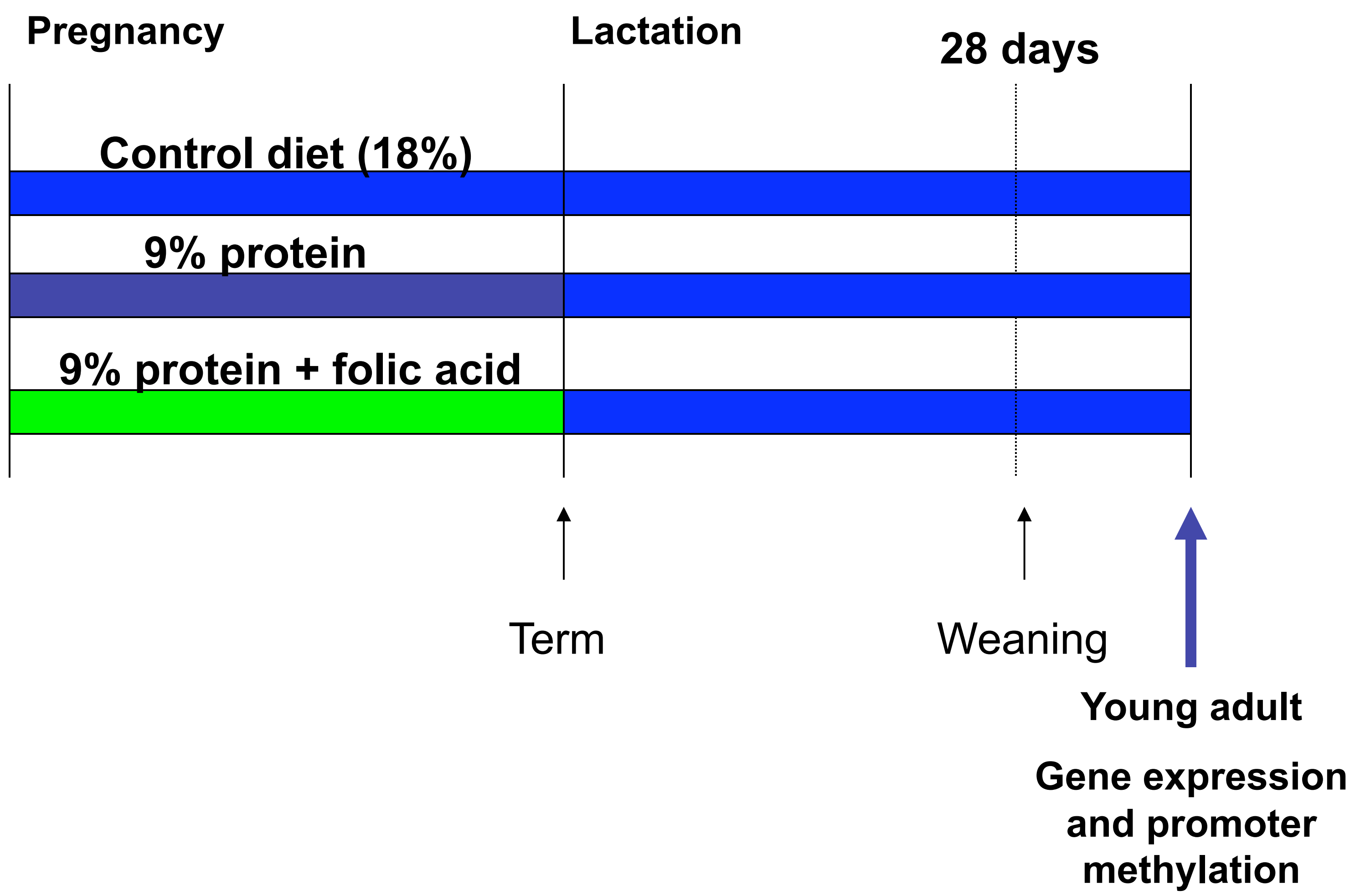


Retinoid X Receptors

- Nuclear receptors- enhance binding of partners (PPAR, LXRs, Vit D receptors) – multiple metabolic roles.

- **Diminished RXRA expression in visceral white adipose tissue from obese mice** (Lefebvre B, *et al* J Clin Invest. 2010;120:1454-68)
- **The liver X-receptor (heterodimer of RXRA) gene promoter is hypermethylated in a mouse model of prenatal protein restriction (**Van Straten *et al* Am J Physiol (Regul Integr Comp Physiol) 2010;298:R275-82

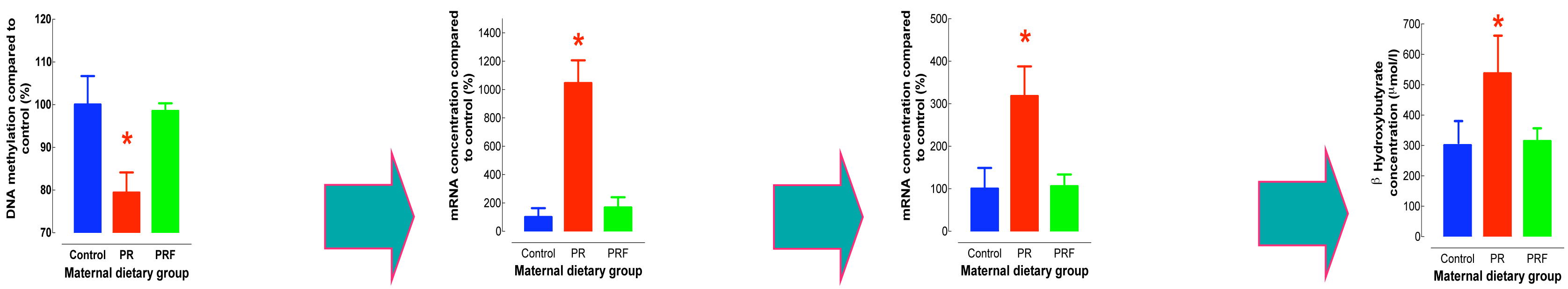
Testing the epigenetic hypothesis



Low protein diet induces, and folic acid prevents, altered epigenetic regulation

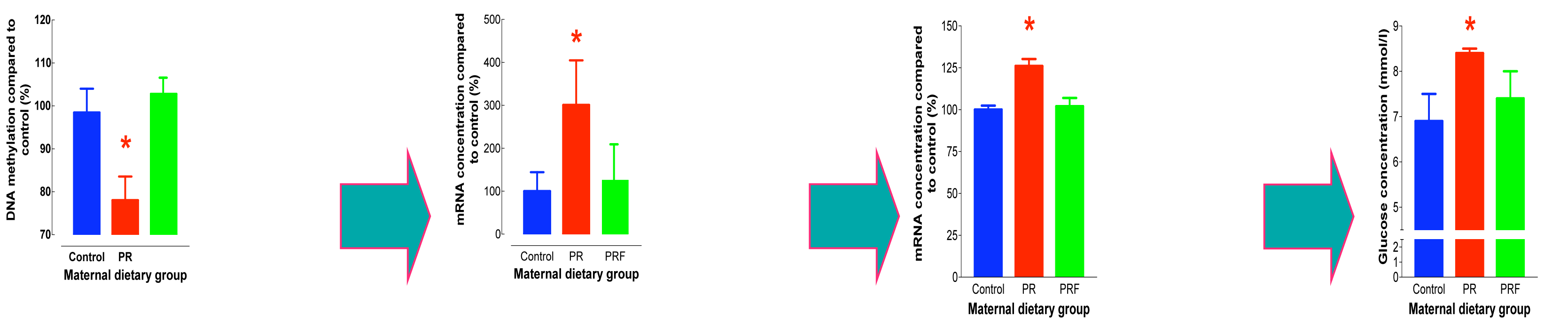
PPARα

Methylation | mRNA expression | AOX expression | β oxidation

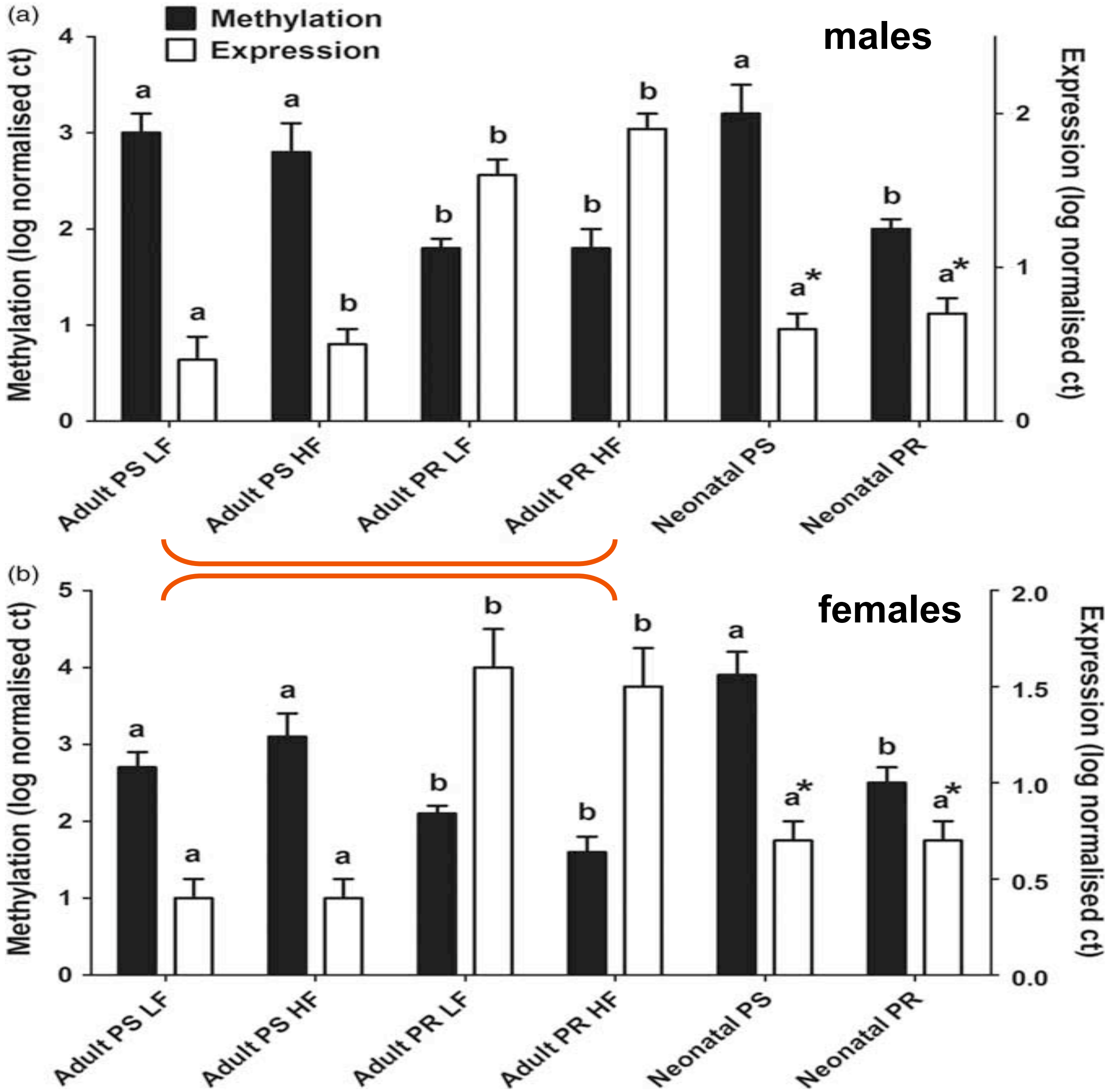


GR

Methylation | mRNA expression | PEPCK expression | Gluconeogenesis



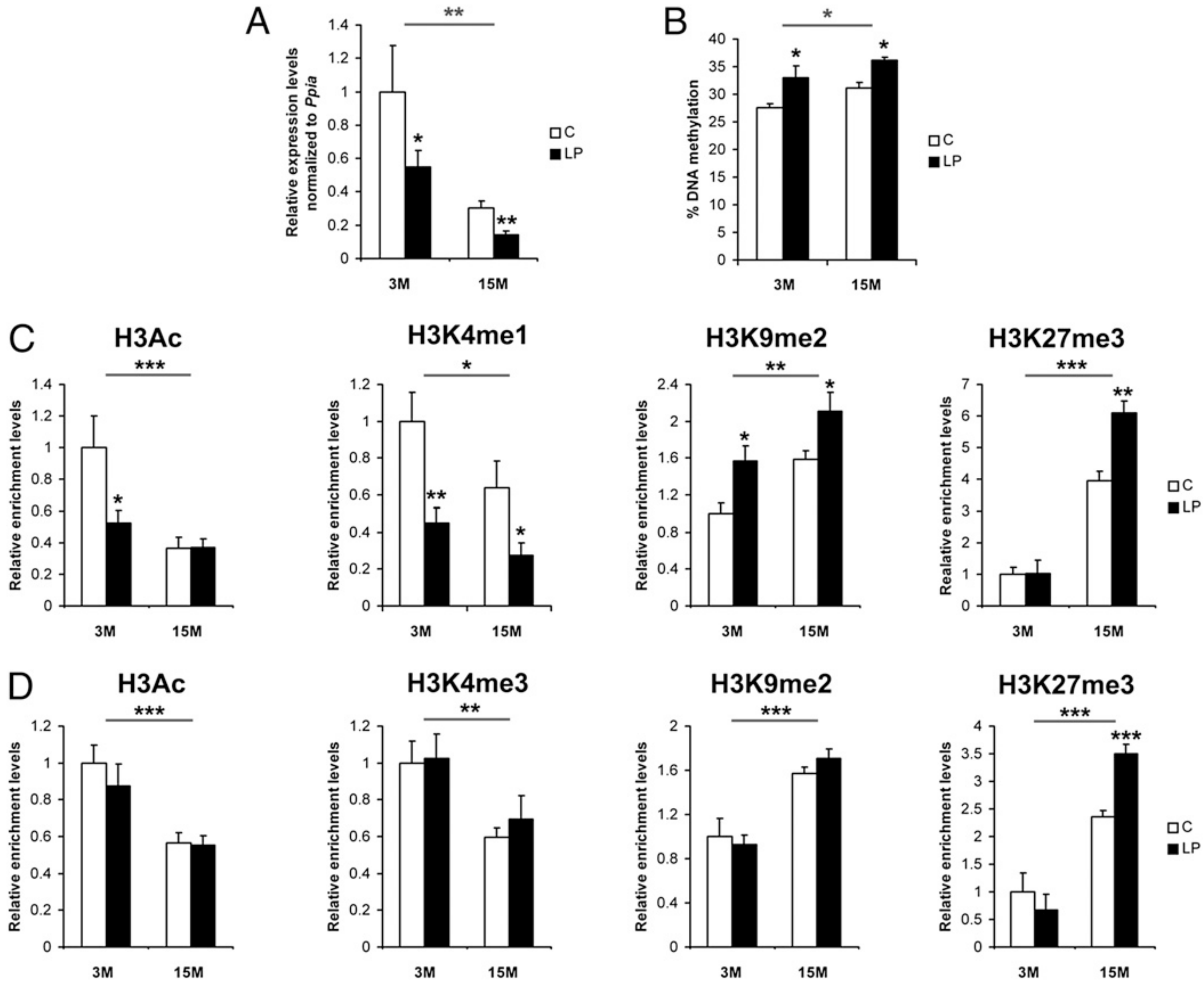
Lillycrop et al. 2007, Burdge et al. 2007



PPARα promoter methylation and gene expression in heart.

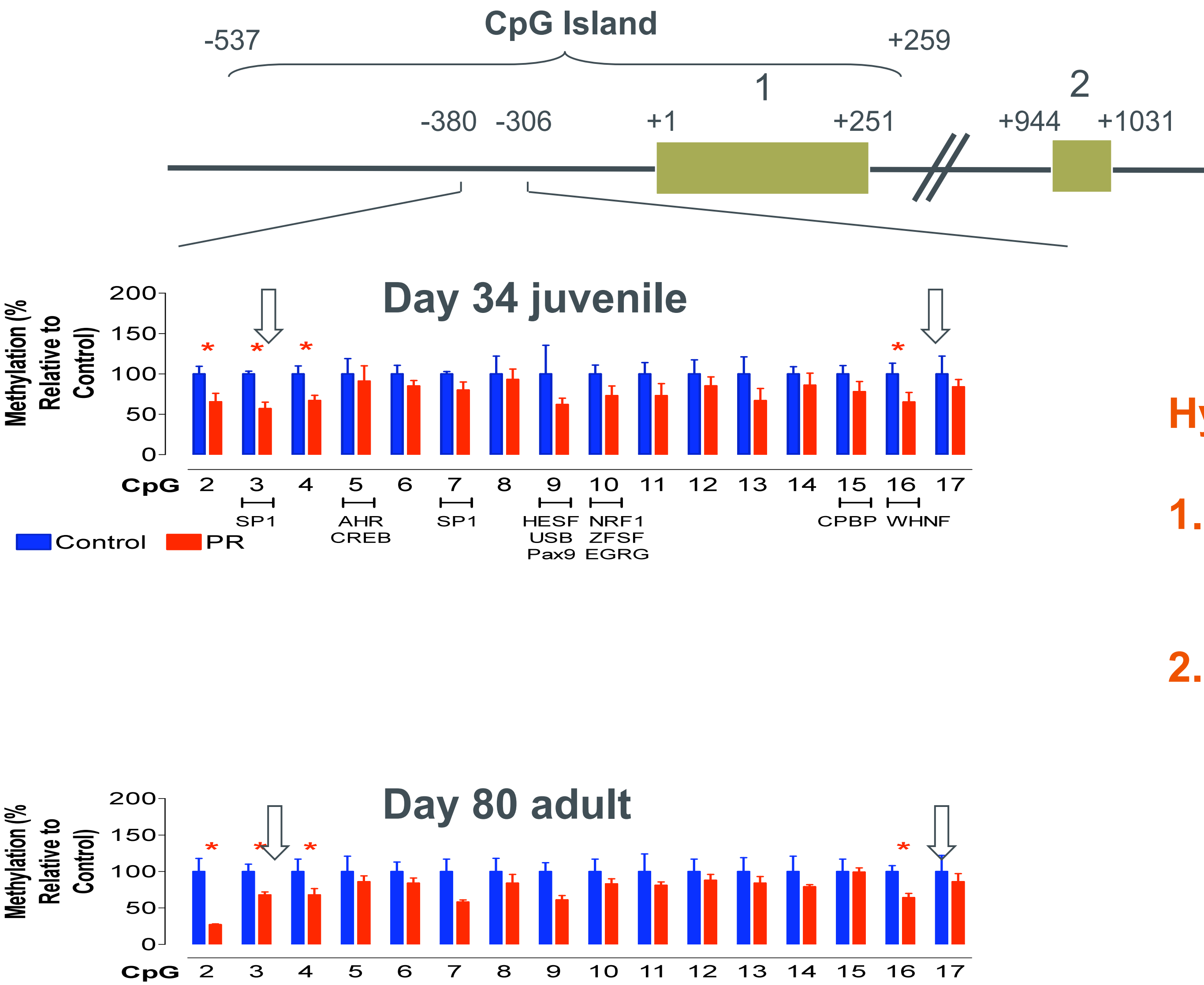
Slater-Jeffries et al

***J DOHaD* 2010**



Early diet- and aging-associated effects on transcriptional activity and epigenetic regulation at the Hnf4a locus in rat islets. Sandovici et al PNAS (2011).

Maternal diet alters methylation of specific CpGs in the PPARα promoter



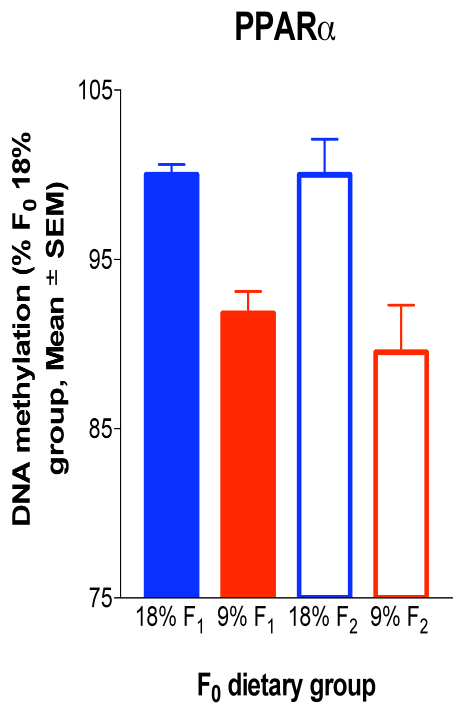
Hypomethylation:-

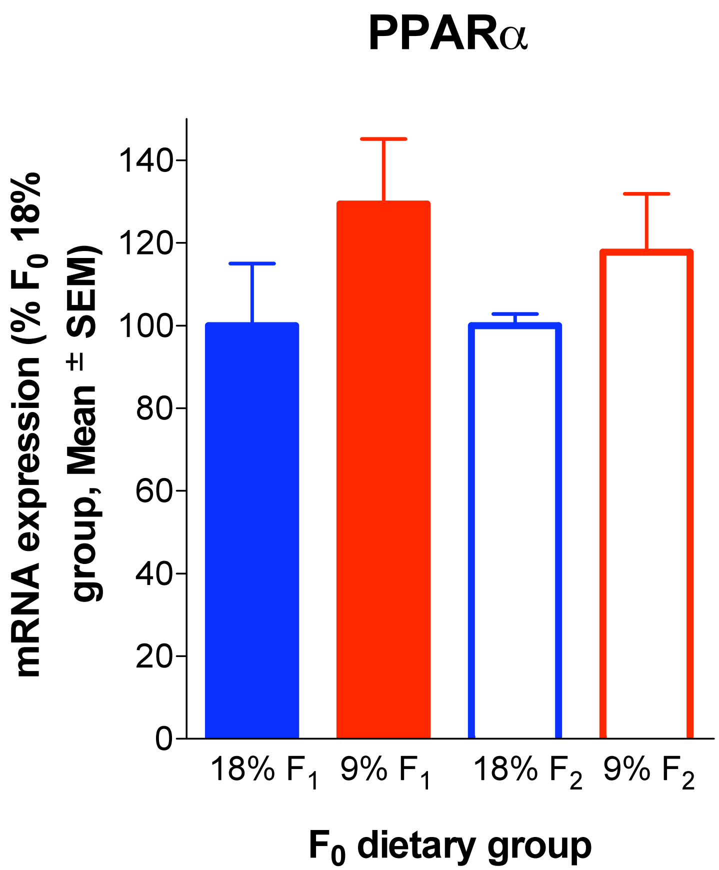
1. **Specific to individual CpGs.**

2. **Persists in adulthood.**

Lillycrop et al. B J Nut 2008

Transgenerational Effects





Burdge et al. 2007

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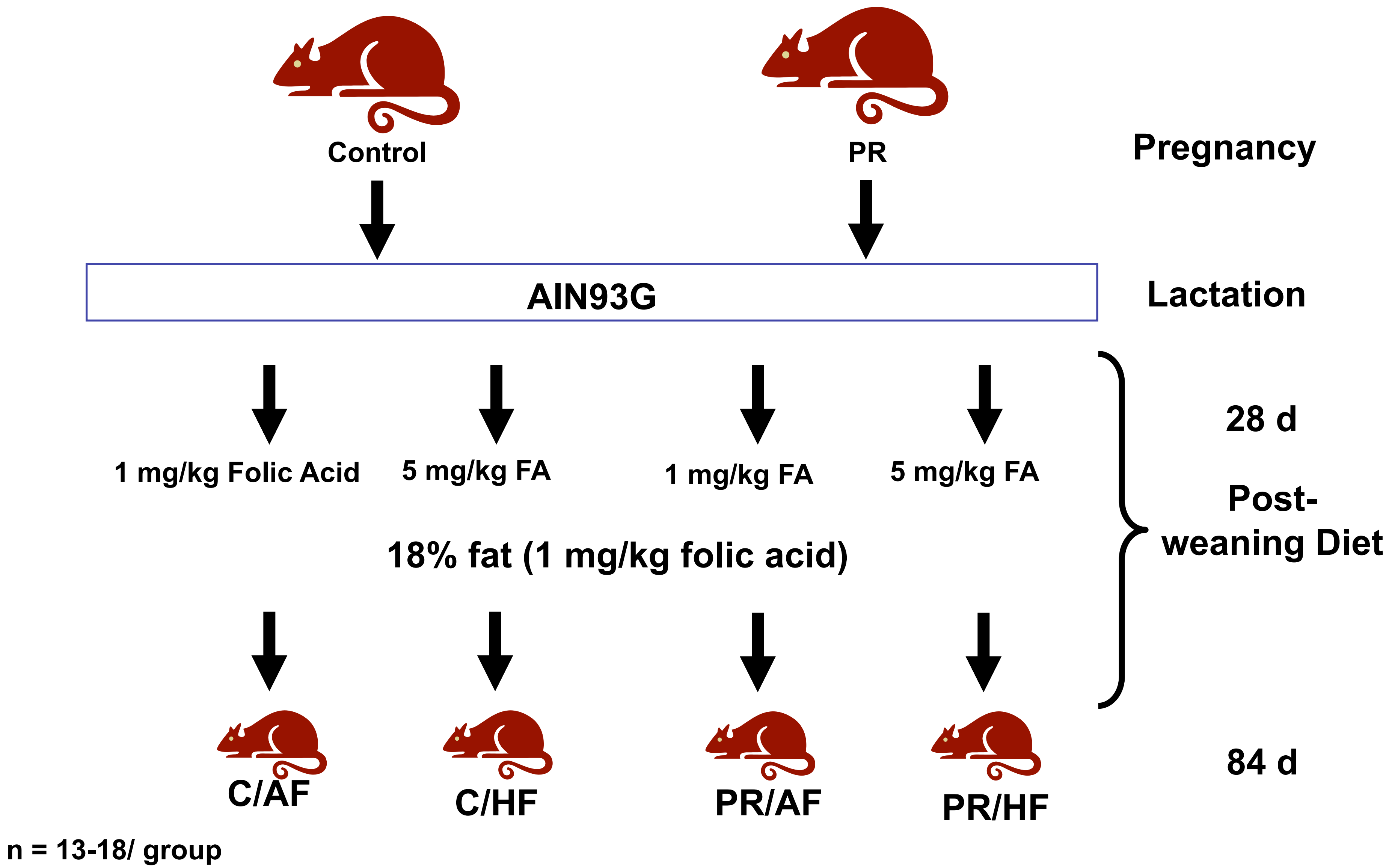
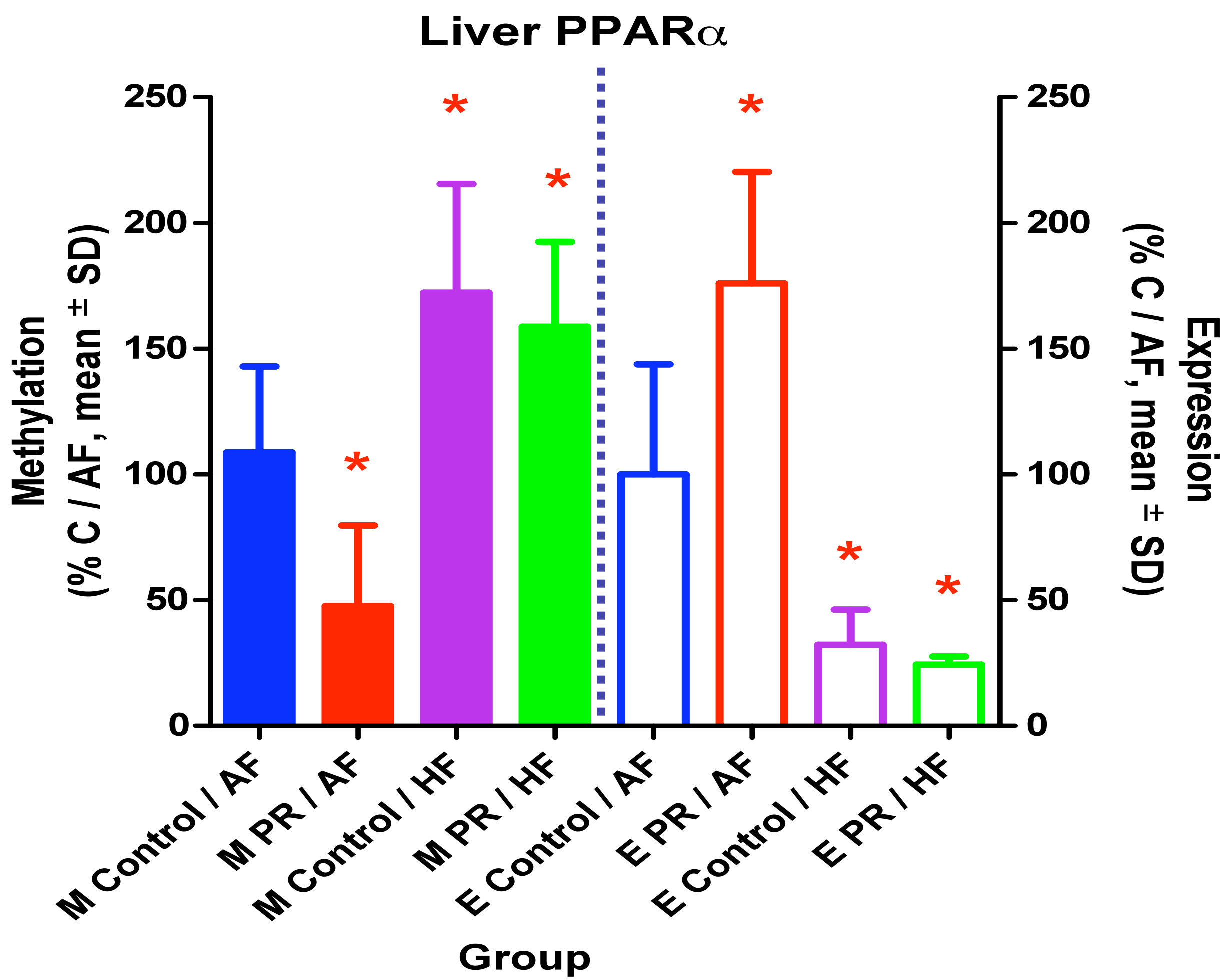
When does plasticity end?



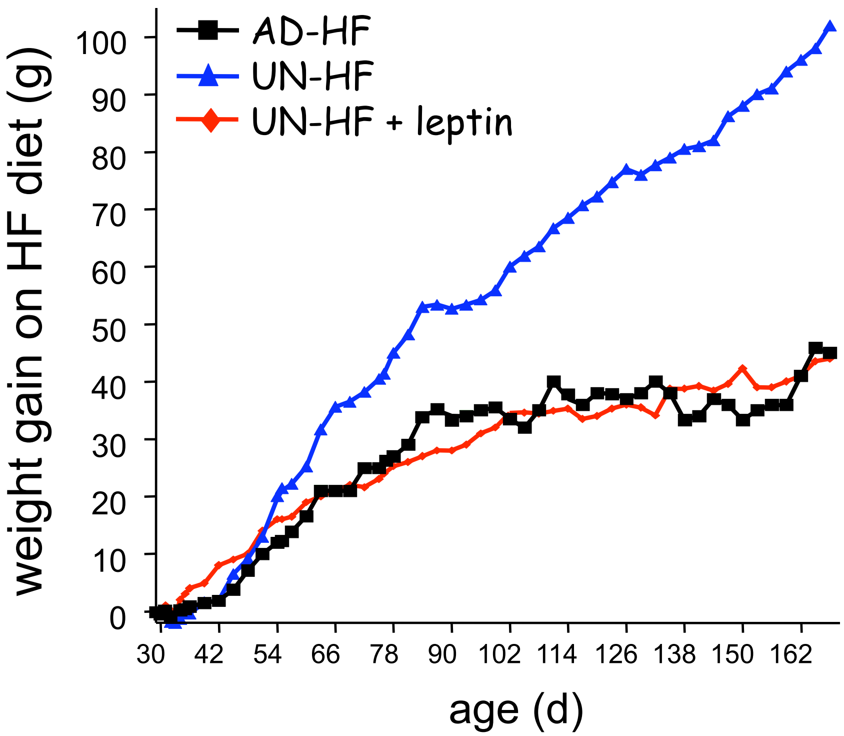
Effect of post-weaning folic acid supplementation on DNA methylation and gene expression



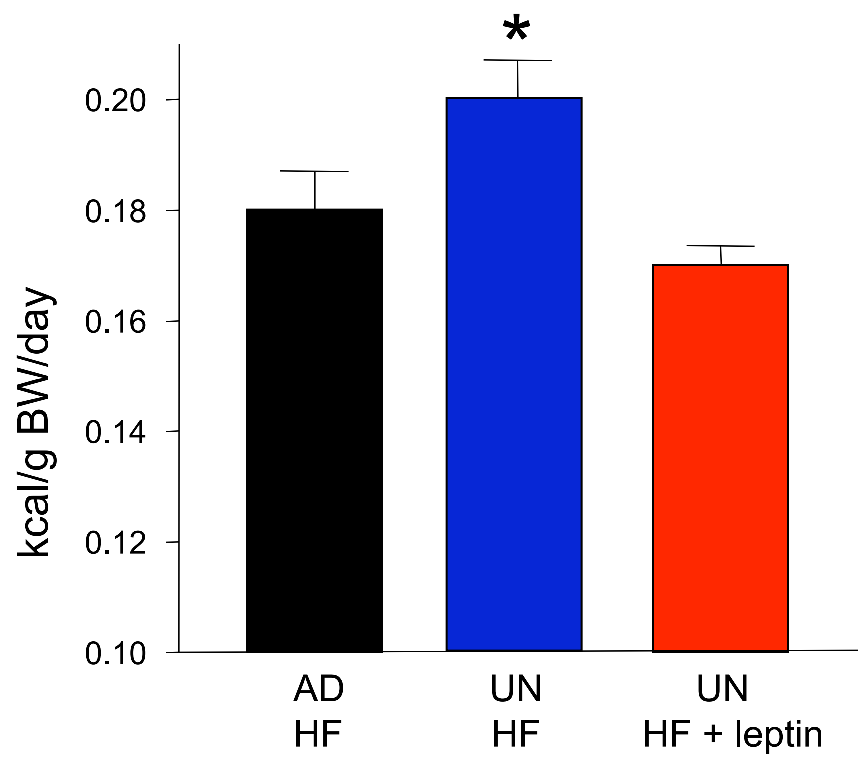
Burdge et al. J. Nutr. 139: 1054–1060, 2009

Early postnatal leptin treatment alleviates the obesogenic effects of post weaning high fat (HF) diet in rat offspring

weight gain on HF vs chow diet

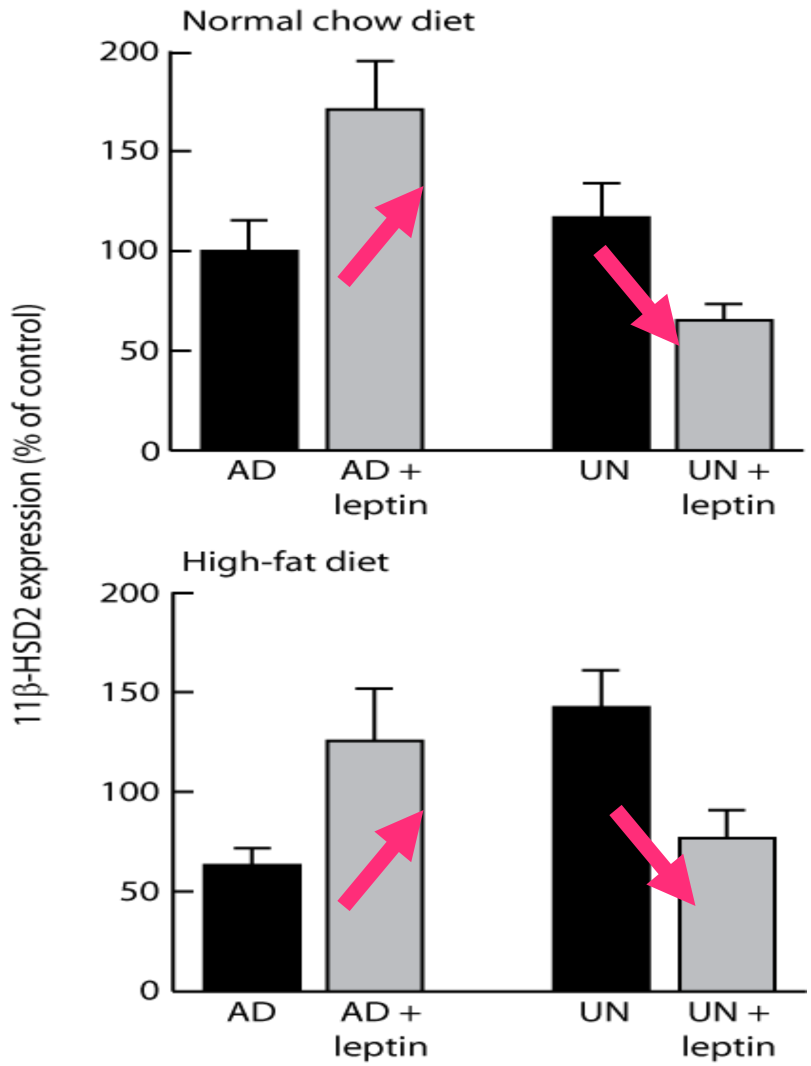


caloric intake

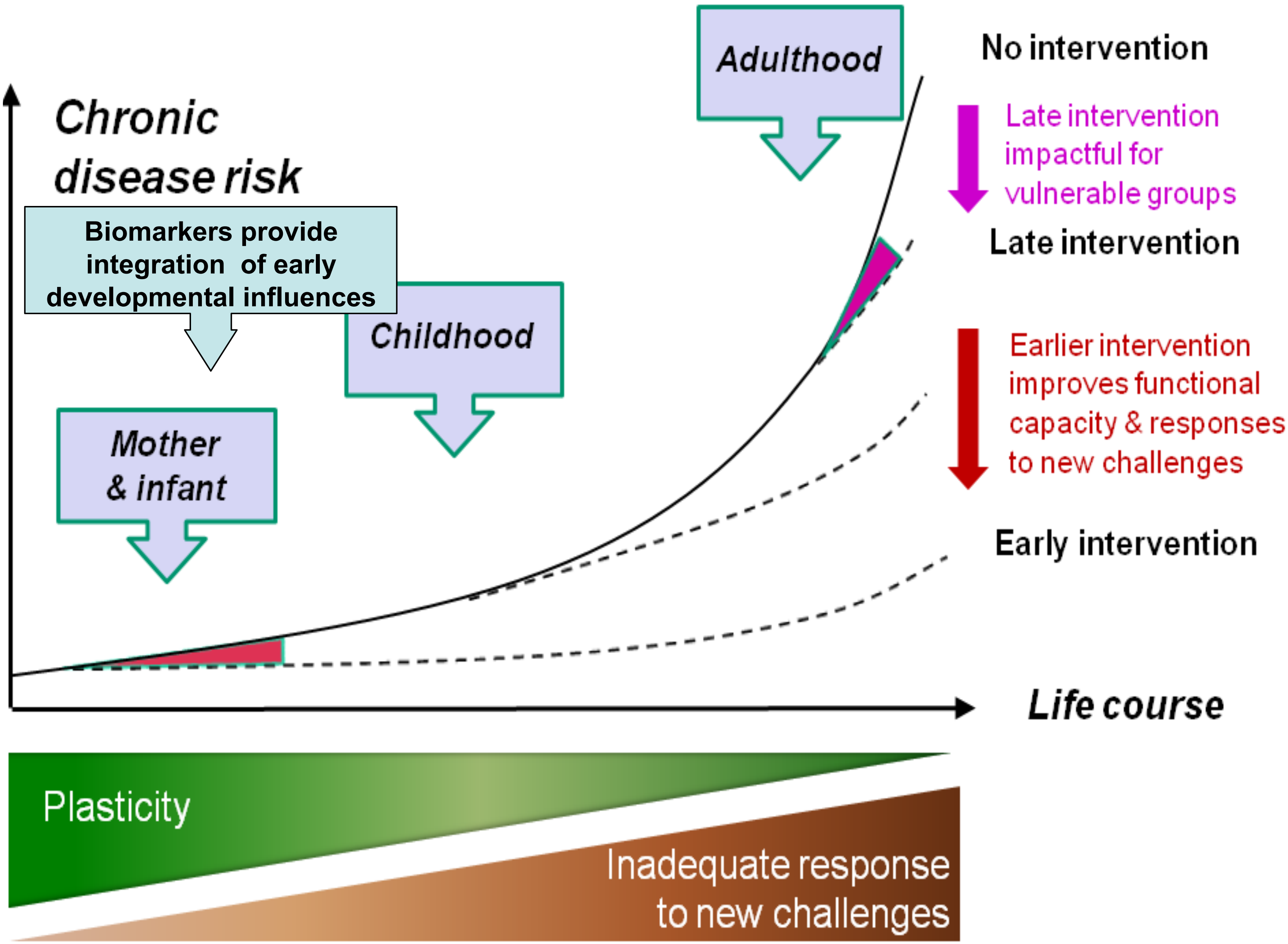


modified from Vickers *et al.* 2005 Endocrinology

Life-long effects of neonatal leptin are directionally dependent on nutrition *in utero*



Gluckman PD, et al. Metabolic plasticity during mammalian development is directionally dependent on early nutritional status. Proc Natl Acad Sci 2007.


Adulthood
No intervention
Chronic disease risk
Late intervention impactful for vulnerable groups
Late intervention
Biomarkers provide integration of early developmental influences
Childhood
Earlier intervention improves functional capacity & responses to new challenges
Mother & infant
Early intervention
Life course
Plasticity
Inadequate response to new challenges