The Epigenetics of Obesity: Individual, Social, and Environmental Influences

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Agricultural Research Service
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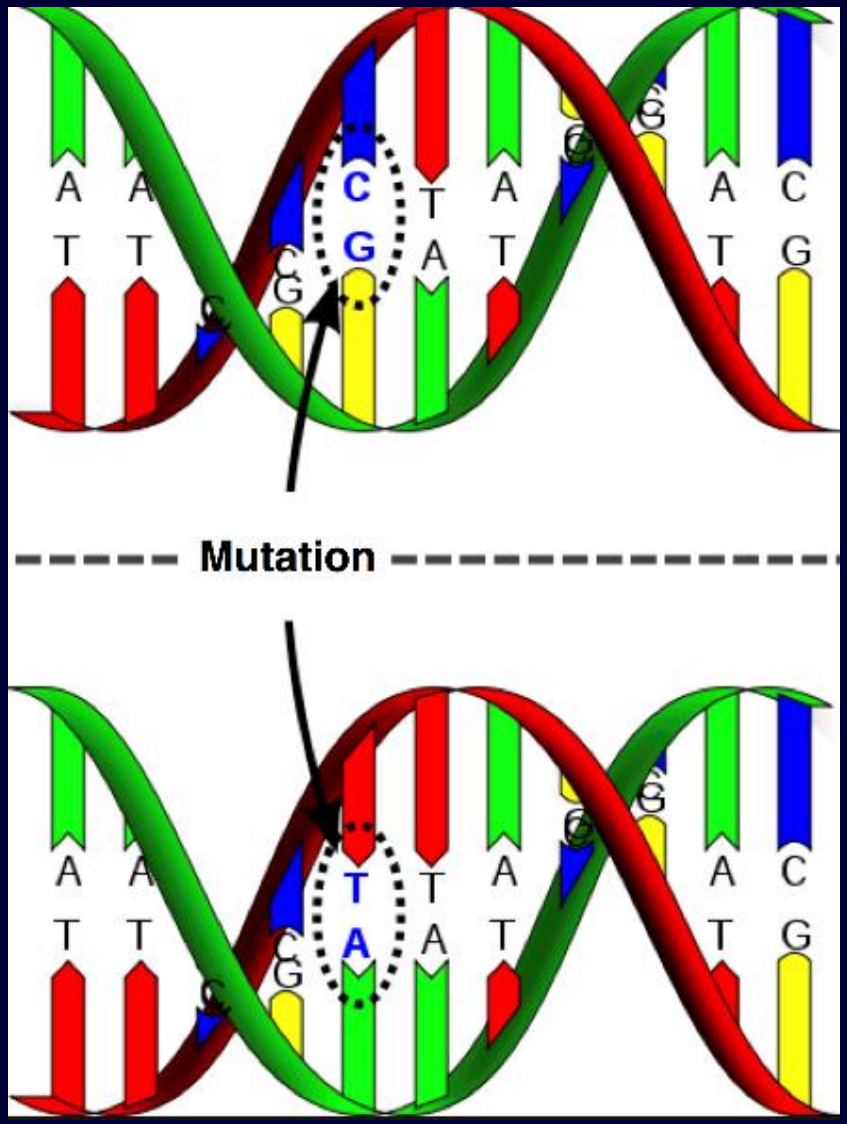
What can happen to our gene(s) that would cause obesity?

Modification via Epigenetic alterations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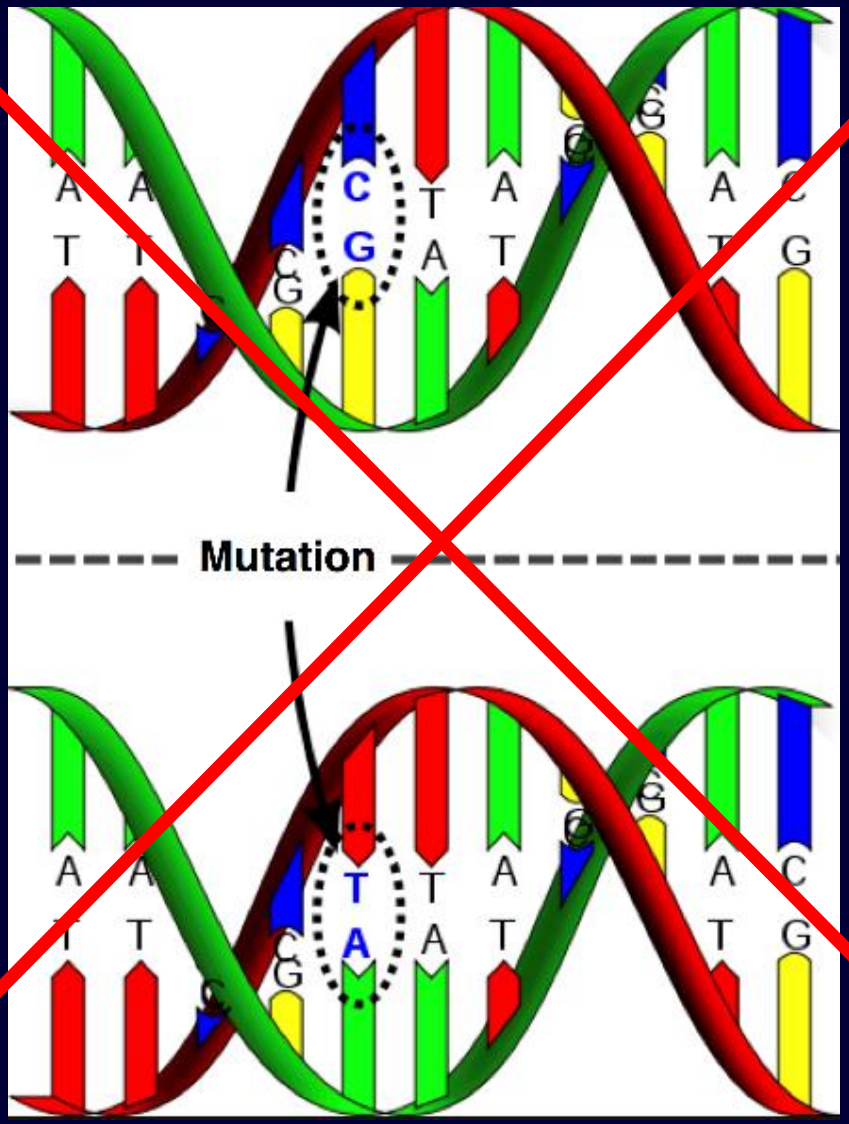
C
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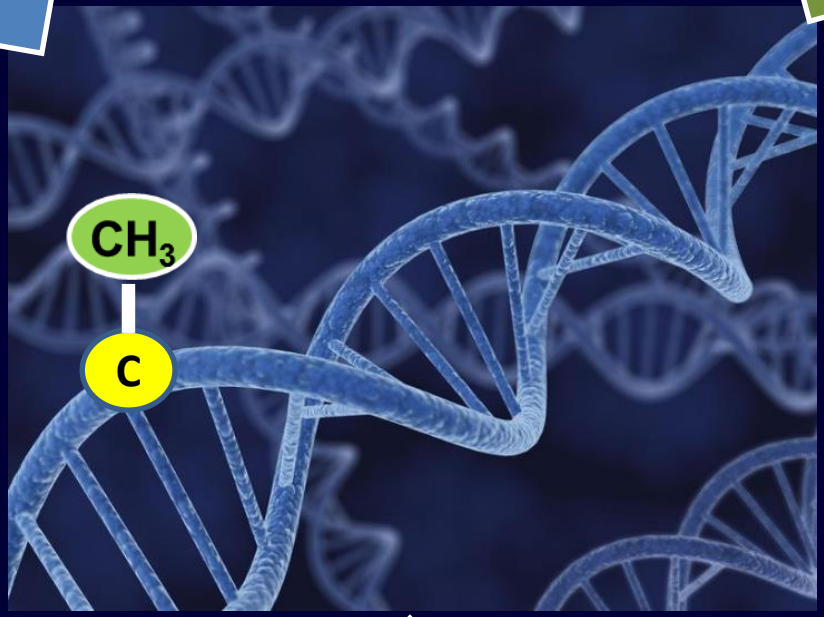
Individual Influences

Environmental Influences

Social Influences

Individual Influences

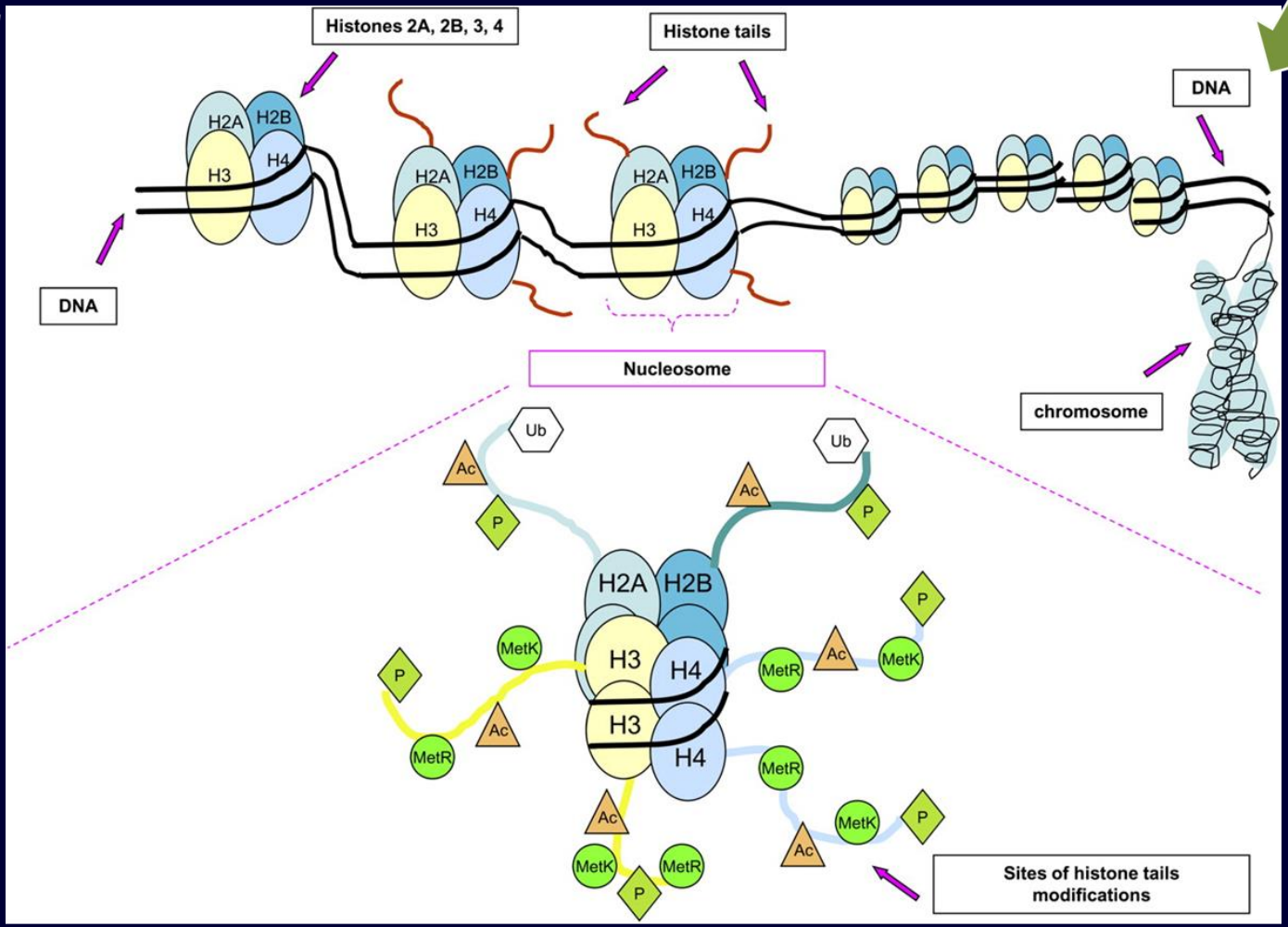
Environmental Influences



Social Influences

Individual Influences

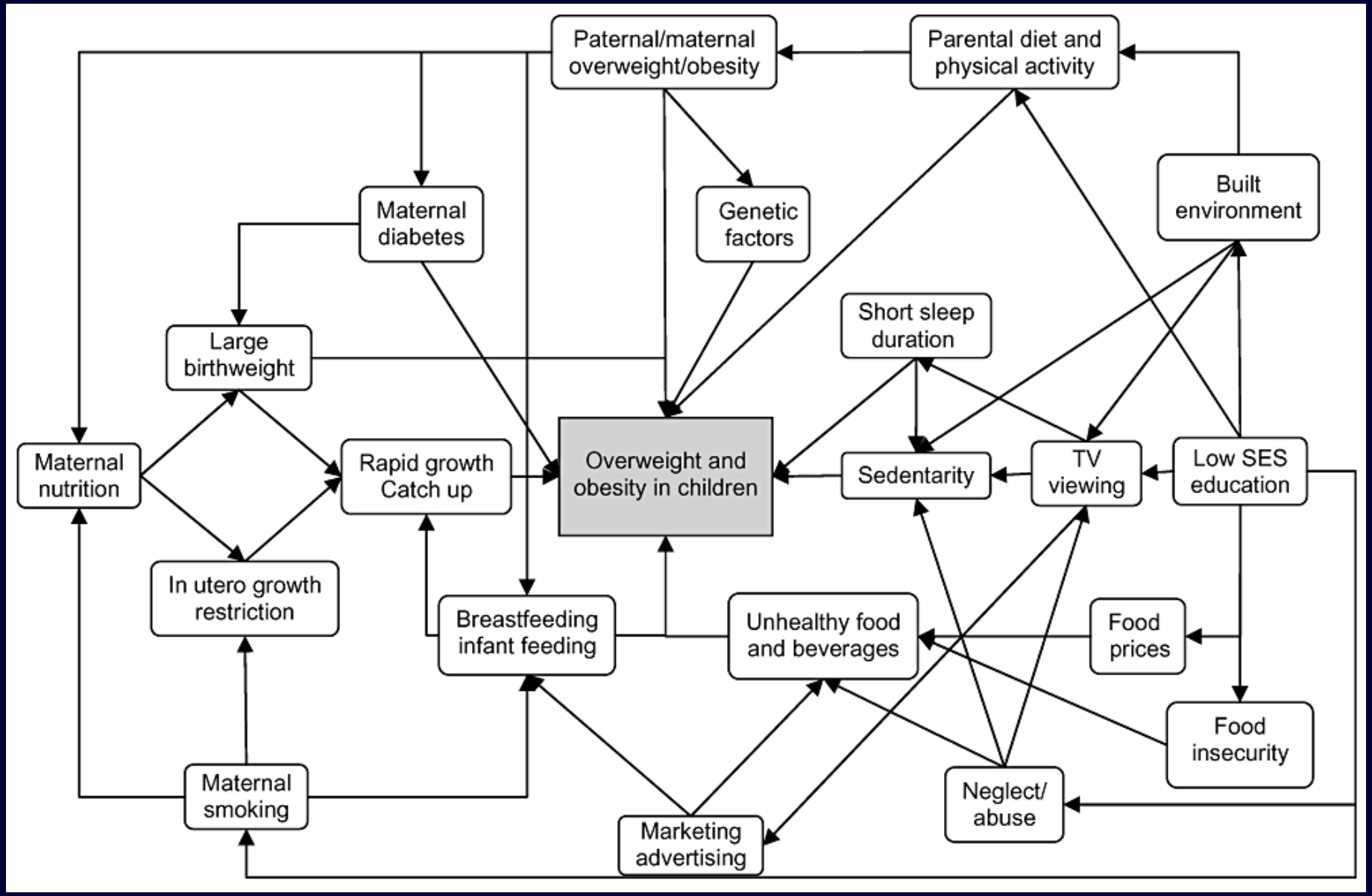
Environmental Influences



Choi and Friso, Adv Nutr, 1:8-16, 2010

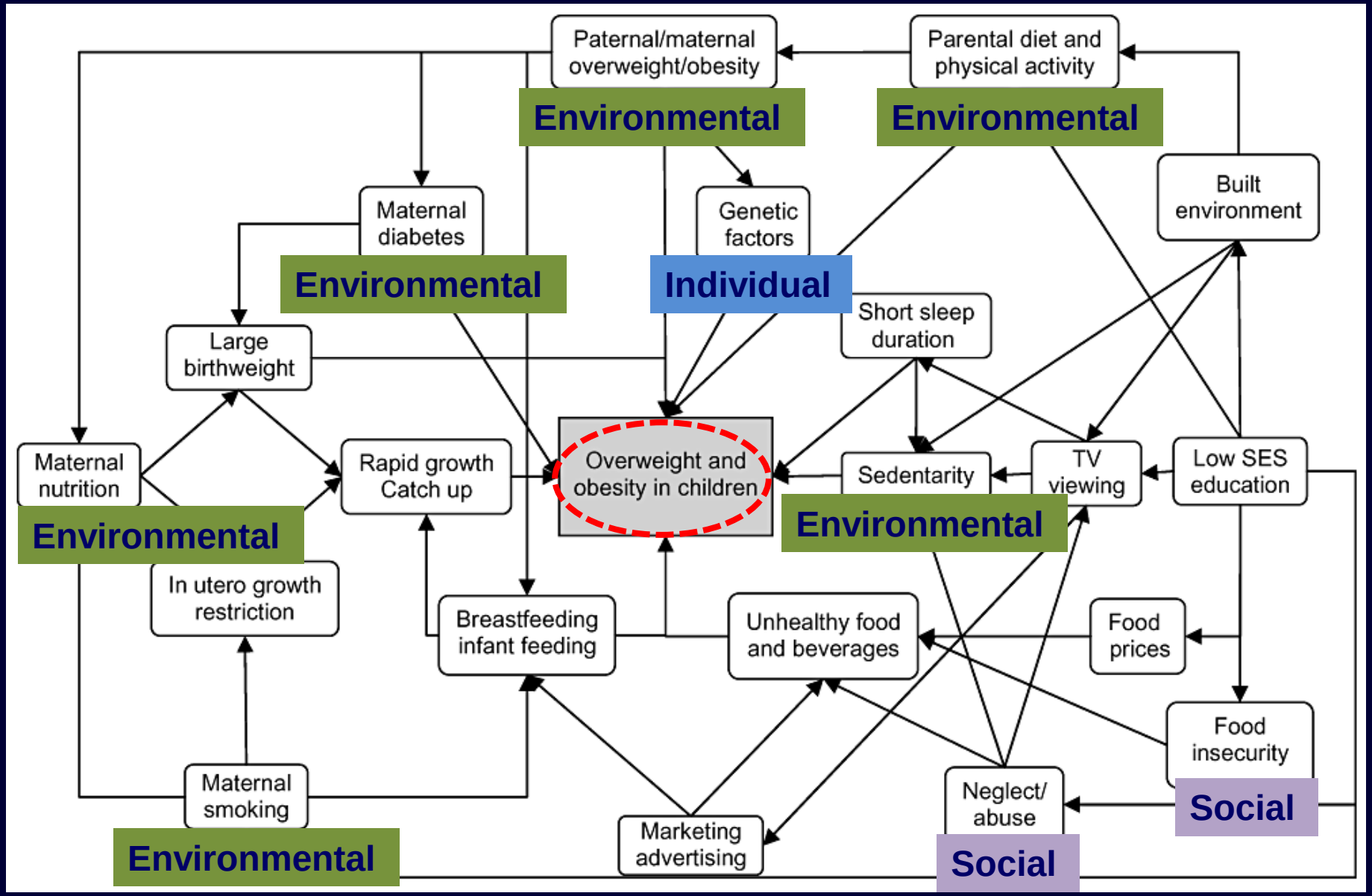
Social Influences

Early-life determinants of overweight and obesity



Obesity Reviews, Monasta et al., 11 (10): 695-708, 2010

Early-life determinants of overweight and obesity



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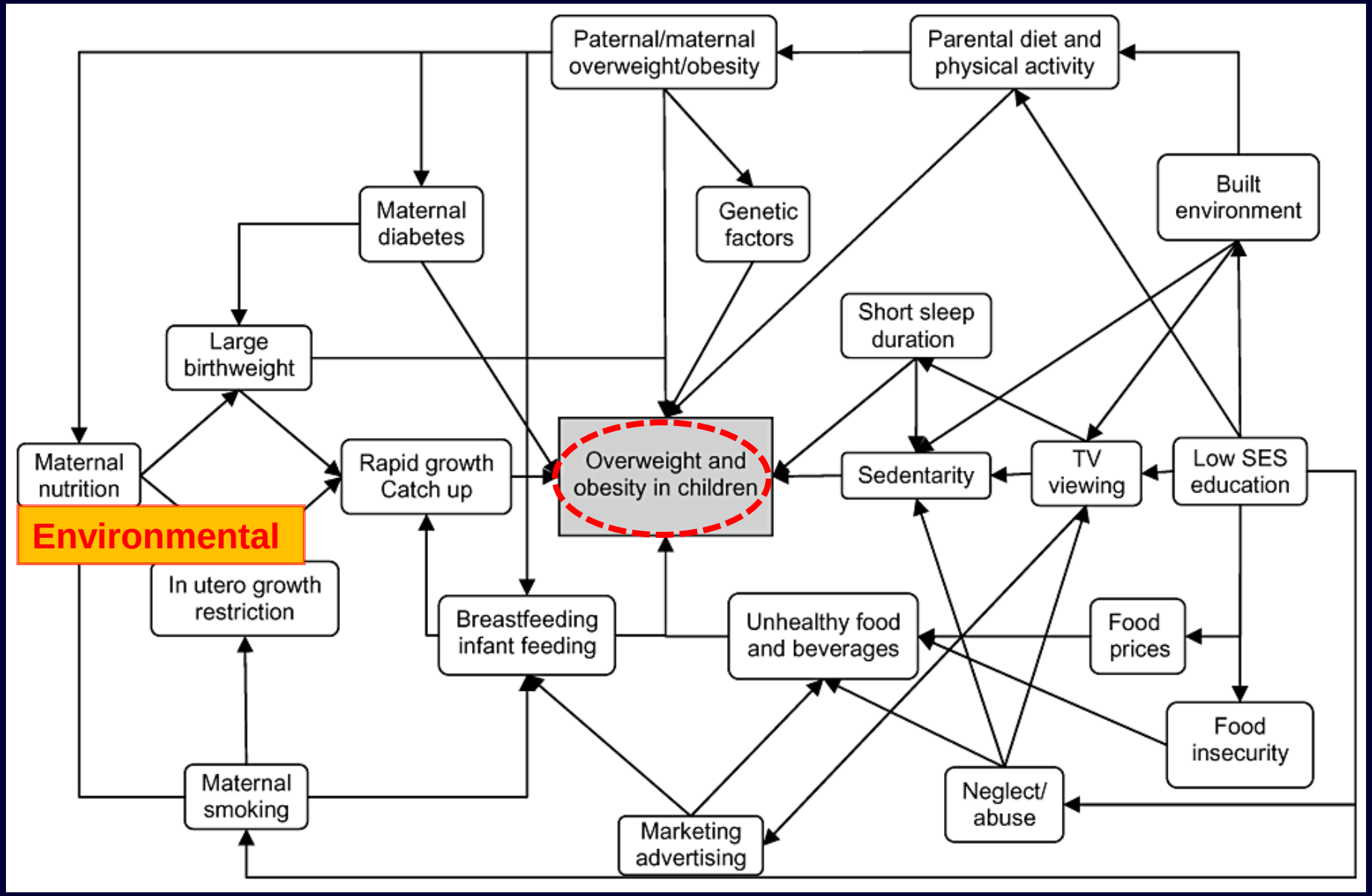
Early-life determinants of overweight and obesity



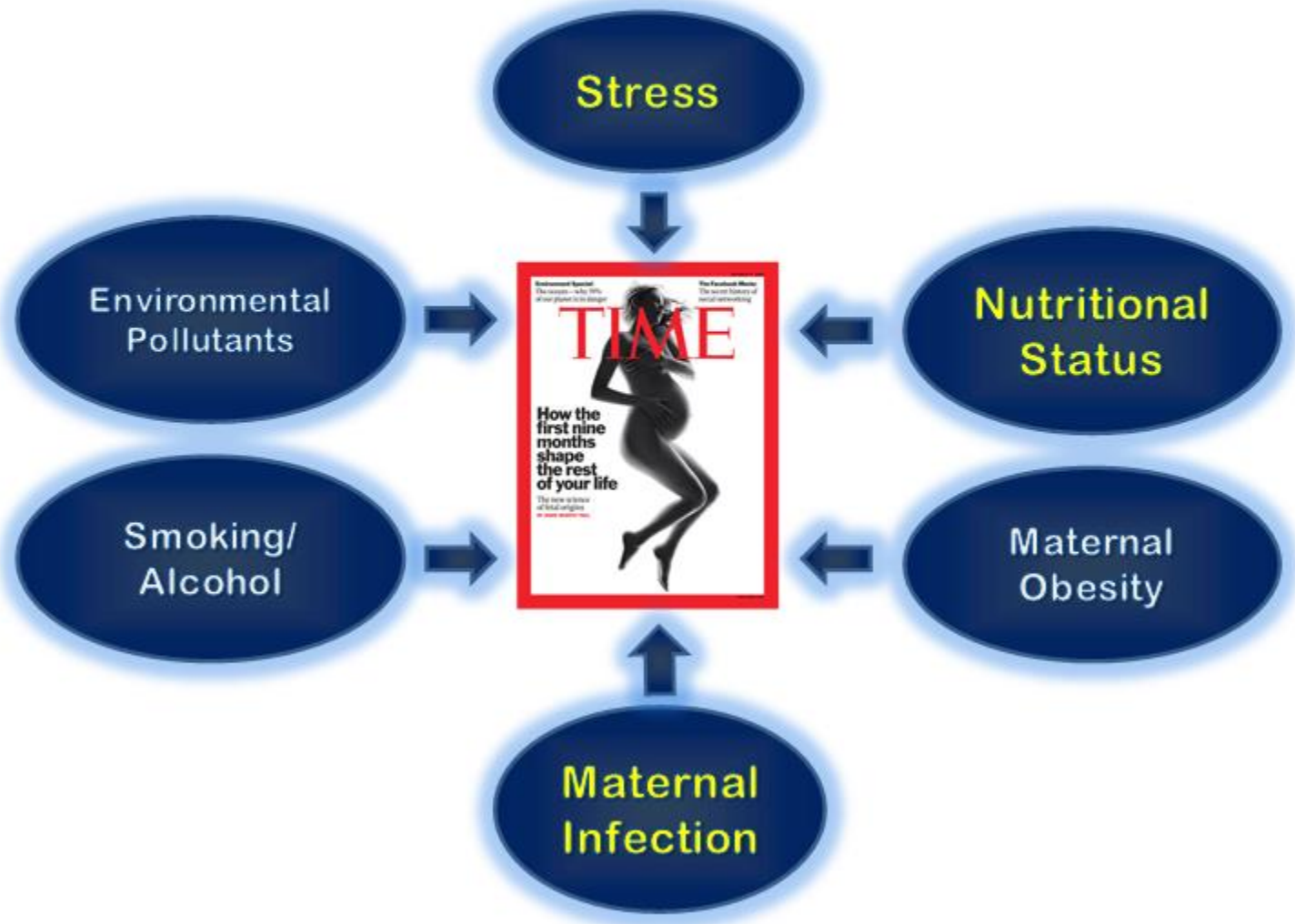
Obesity Reviews, Monasta et al., 11 (10): 695-708, 2010

Epigenetics

- Epigenetics is an **inheritable changes** that affects gene expression without DNA base pair sequence changes

- Examples of epigenetic phenomena
  - DNA methylation
  - histone modifications
  - chromatin remodeling

Maternal diet, infection, stress and inflammatory immune function regulation



nature REVIEWS ENDOCRINOLOGY

NATURE REVIEWS ENDOCRINOLOGY | RESEARCH HIGHLIGHT

REPRODUCTIVE ENDOCRINOLOGY

You are what your grandmother ate—inherited effects of *in utero* undernourishment

Jennifer Sargent

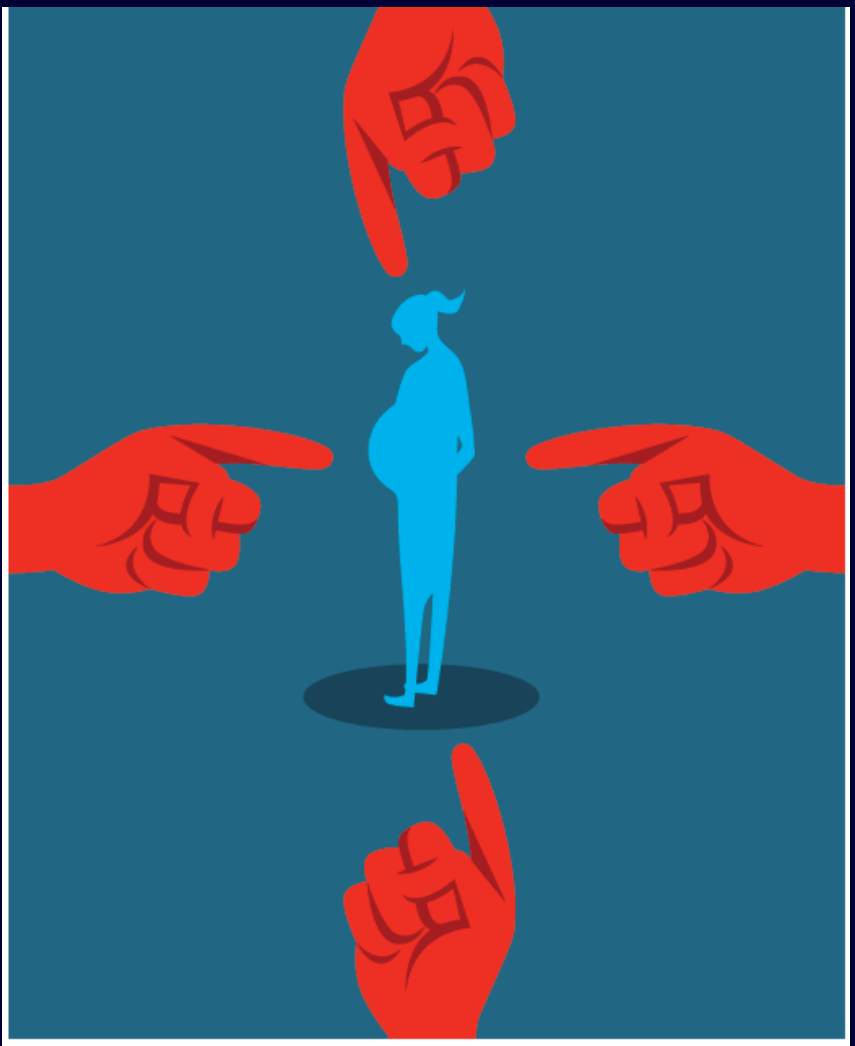
Nature Reviews Endocrinology **10**, 509 (2014) | doi:10.1038/nrendo.2014.127

Published online 29 July 2014

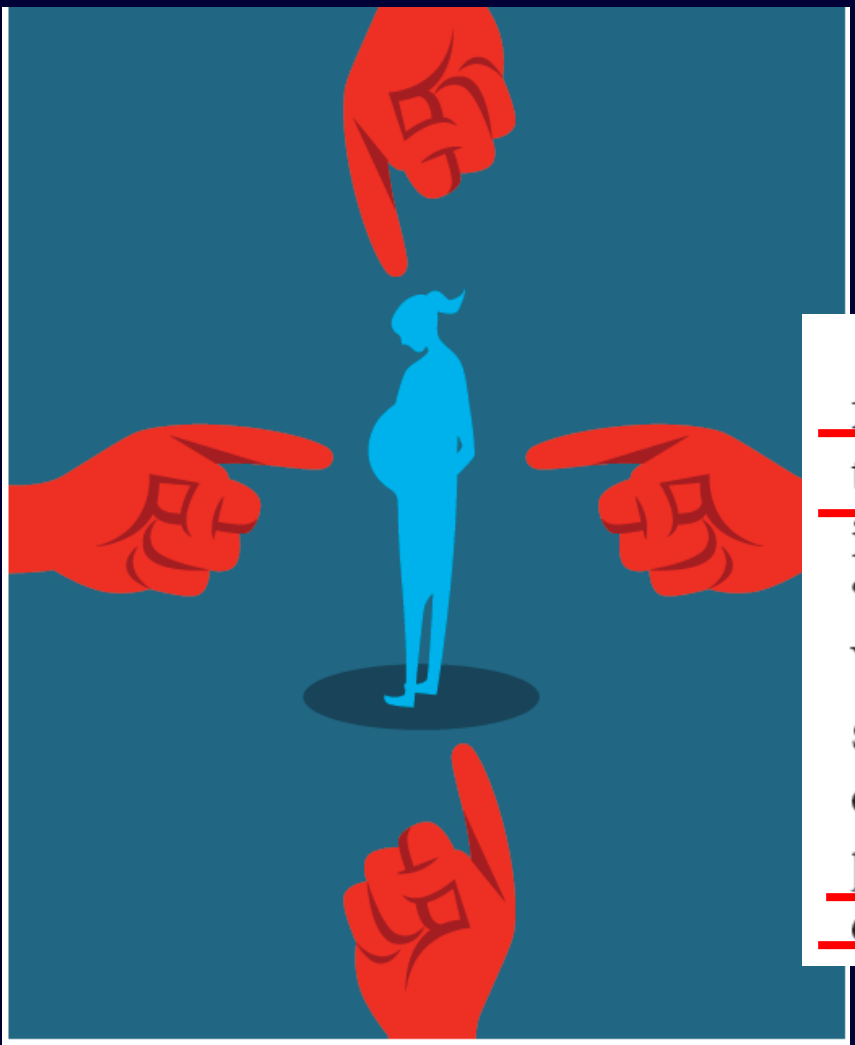
"What your grandparents ate could affect your health"

For example, when a paternal grandmother experienced drastic changes in food availability as a child, then granddaughters had an increased risk for cardiovascular mortality as an adult

Bygren *et al. BMC Genetics* 2014, **15**:12
http://www.biomedcentral.com/1471-2156/15/12

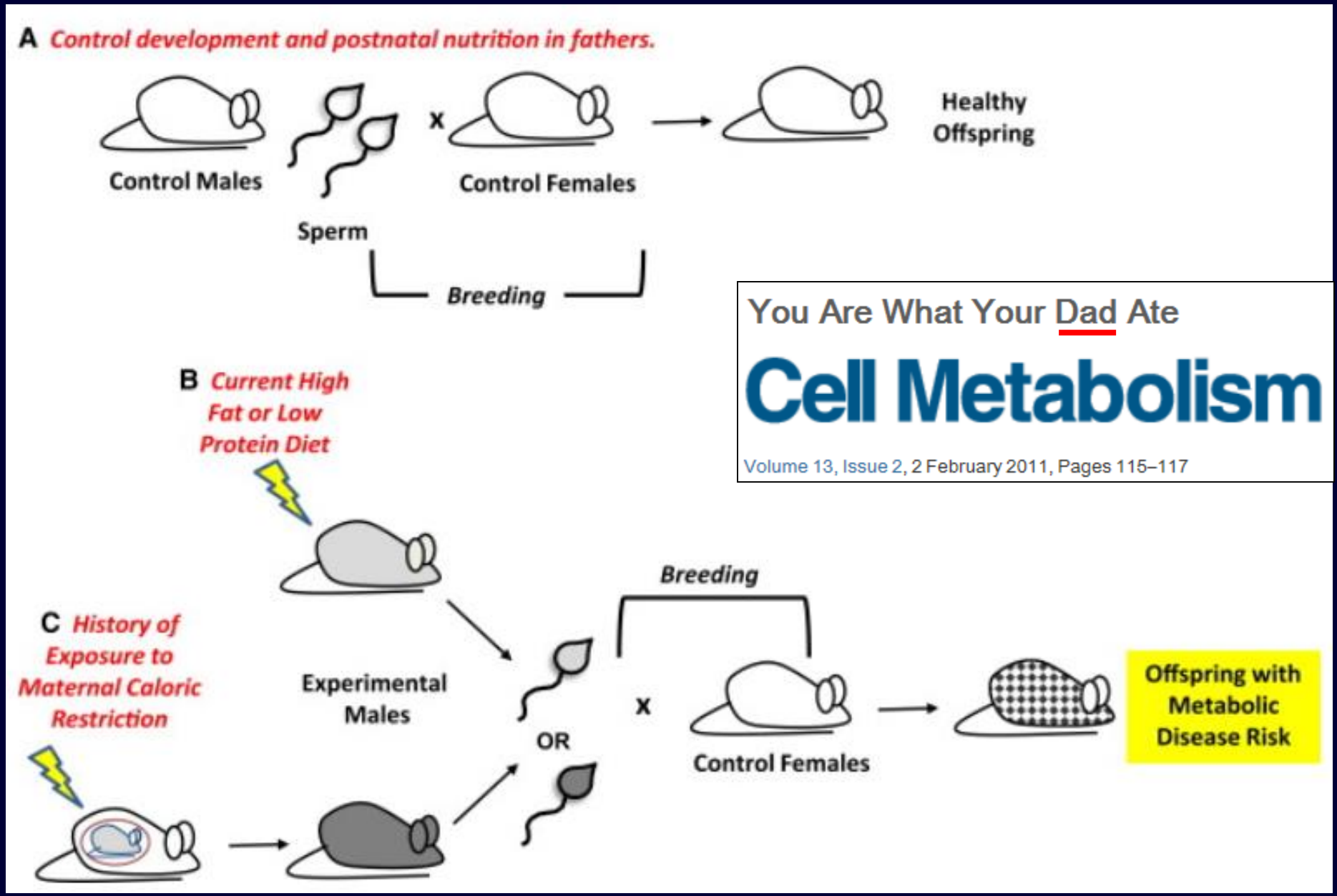


Don’t blame the mothers



Don't blame the mothers

Headlines in the press reveal how these findings are often simplified to focus on the maternal impact: 'Mother's diet during pregnancy alters baby's DNA' (BBC), 'Grandma's Experiences Leave a Mark on Your Genes' (*Discover*), and 'Pregnant 9/11 survivors transmitted trauma to their children' (*The Guardian*). Factors such as the paternal contribution, family life and social environment receive less attention.



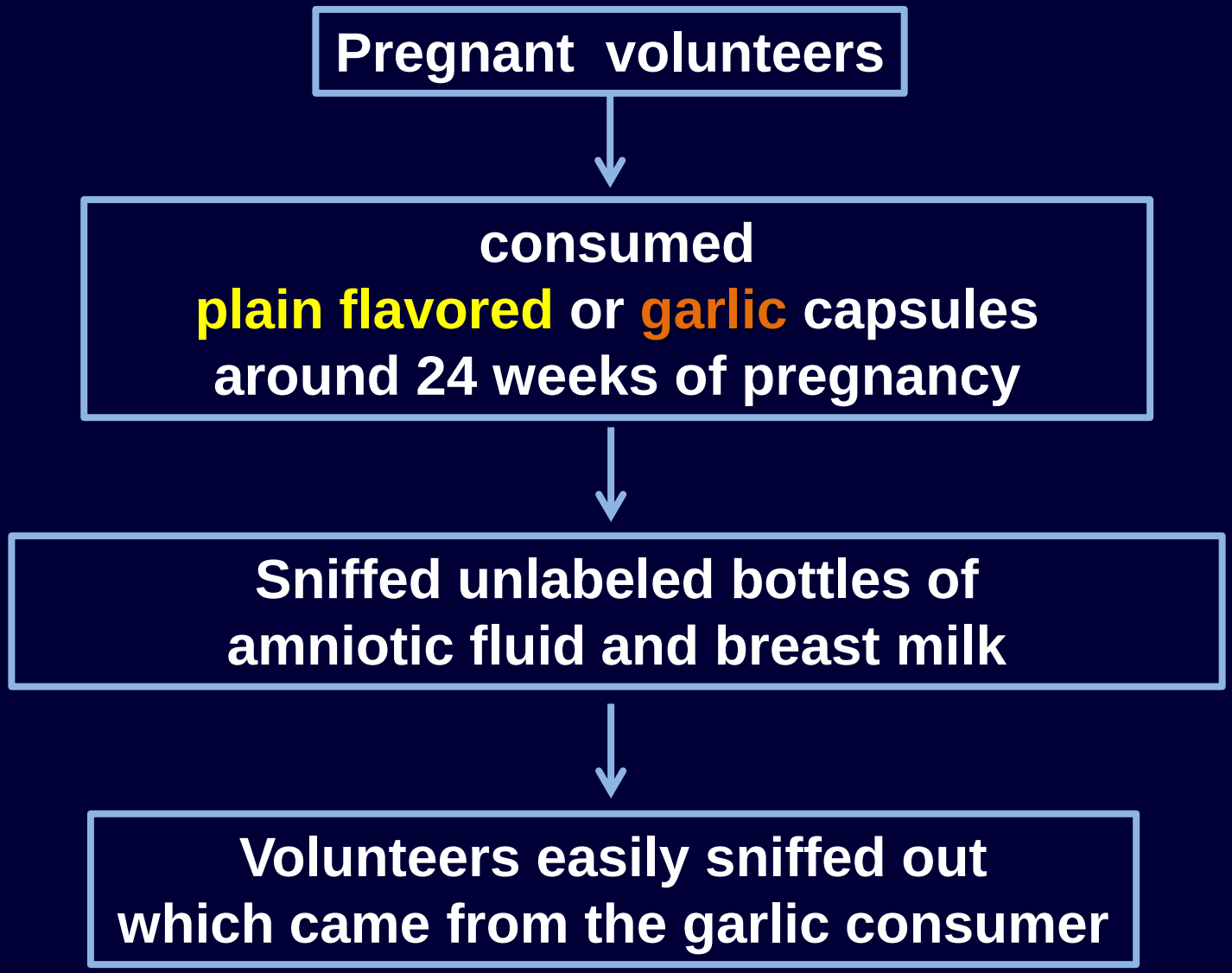
You Are What Your Dad Ate

Cell Metabolism

Volume 13, Issue 2, 2 February 2011, Pages 115–117

Cover, Science, August 15th, 2014, Vol. 345

Do prenatal experiences shape culinary tastes?



Babies born from two groups of volunteers who consumed plain flavored or garlic capsules

Videotape images were generated when babies were given garlic milk

Other Supporting Evidence (Animal Study)

FASEB Journal, 25(7): 2167-2179, 2011

Other supporting evidence (animal study)

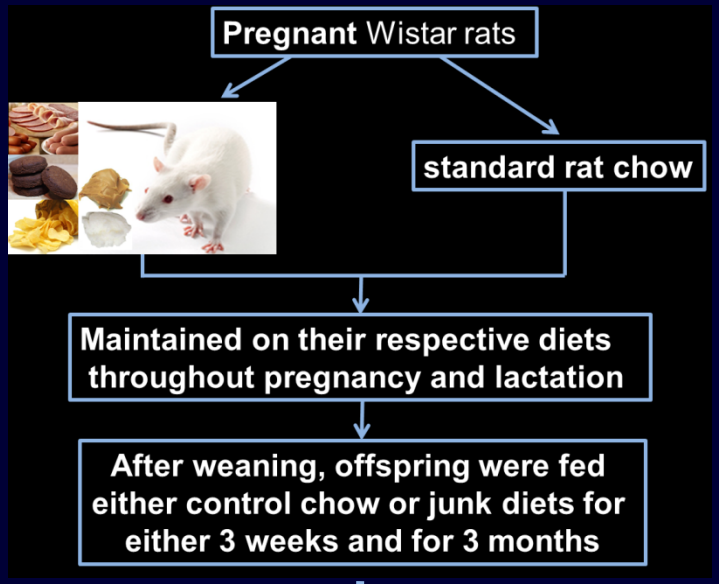
FASEB Journal, 25(7): 2167-2179, 2011

Pregnant Wistar rats

standard rat chow

Maintained on their respective diets throughout pregnancy and lactation

After weaning, offspring were fed either control chow or junk diets for either 3 weeks and for 3 months



Conclusions:

Mice whose mothers had a junk food diet developed altered development of the central reward system, resulting in increased fat intake and altered response of the reward system to excessive junk-food intake in postnatal life

Example of Basic Science Studies of Epigenetics

Obesity and Epigenetics of Adipose tissue

(USDA ARS Research Program)

Large for Gest. Age | Normal | IUGR

LP fed dams and offspring Phenotyes

hypertension (Langley-Evans et al, Clin Nutr 1994; 13: 319–324)

increased fat deposition and altered feeding behavior

(Lucas et al., Br J Nutr 1996; 76: 605–612, Bellinger et al.,
Br J Nutr 2004; 92: 513–520, and
Bellinger et al., Int J Obes (Lond) 2006; 30: 729–738)

impaired glucose homeostasis, dyslipidaemia

(Burdge et al., Prostaglandins Leukot Essent Fatty Acids 2008; 78: 73–79)

impaired immunity

(Calder and Yaqoob, Nutr Res 2000; 20: 995–1005)

increased susceptibility to oxidative stress

(Langley-Evans and Sculley, Mech Ageing Dev 2005; 126: 804–812)

Intrauterine growth restriction and catch-up growth

Maternal under nutrition

Low birth weight

Increased propensity for catch up growth

Normal diet

Normal weight

Normal growth

Sutton et al., Endocrinology 2010;151(4):1570-80

Maternal under nutrition

Low birth weight

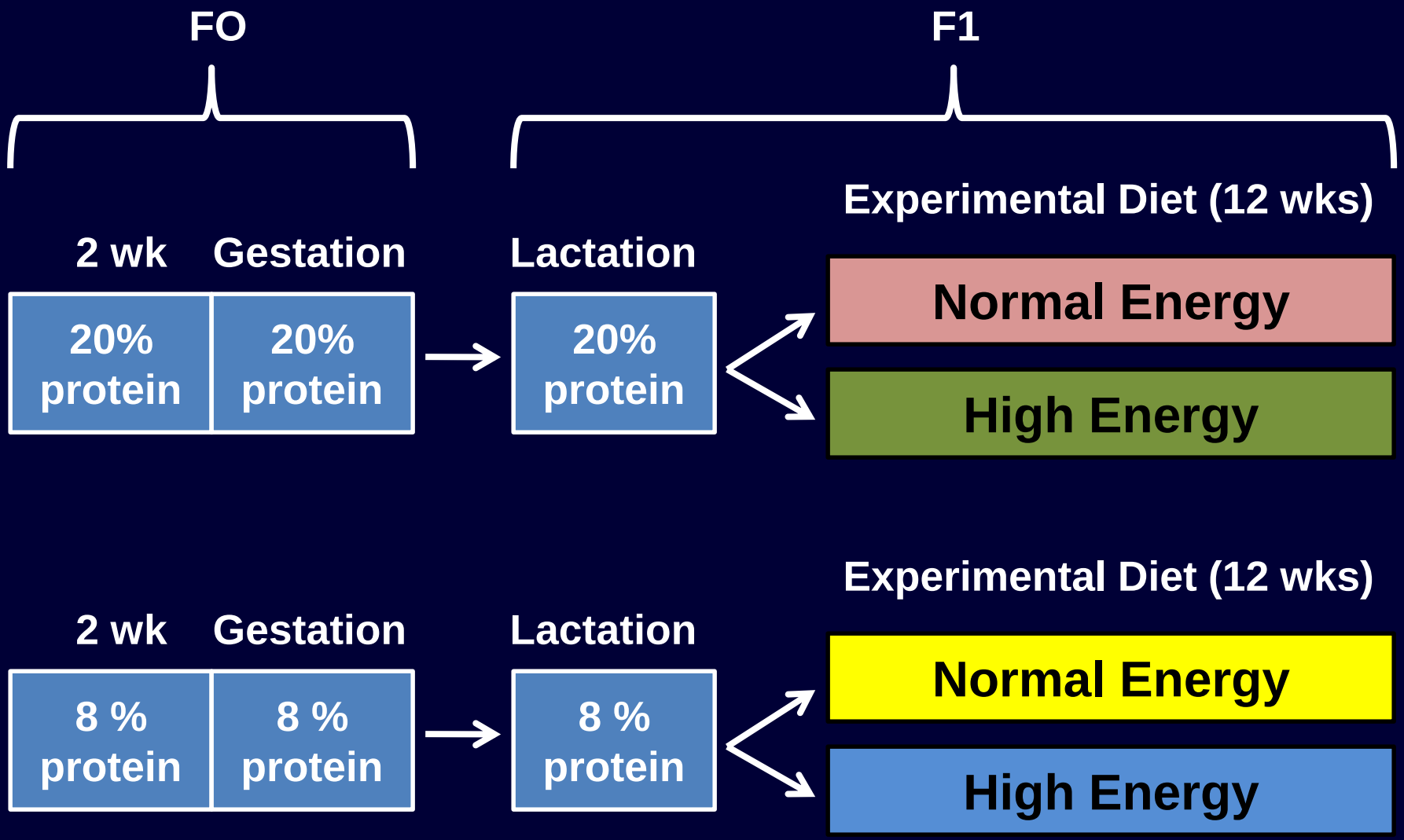
High Fat diet

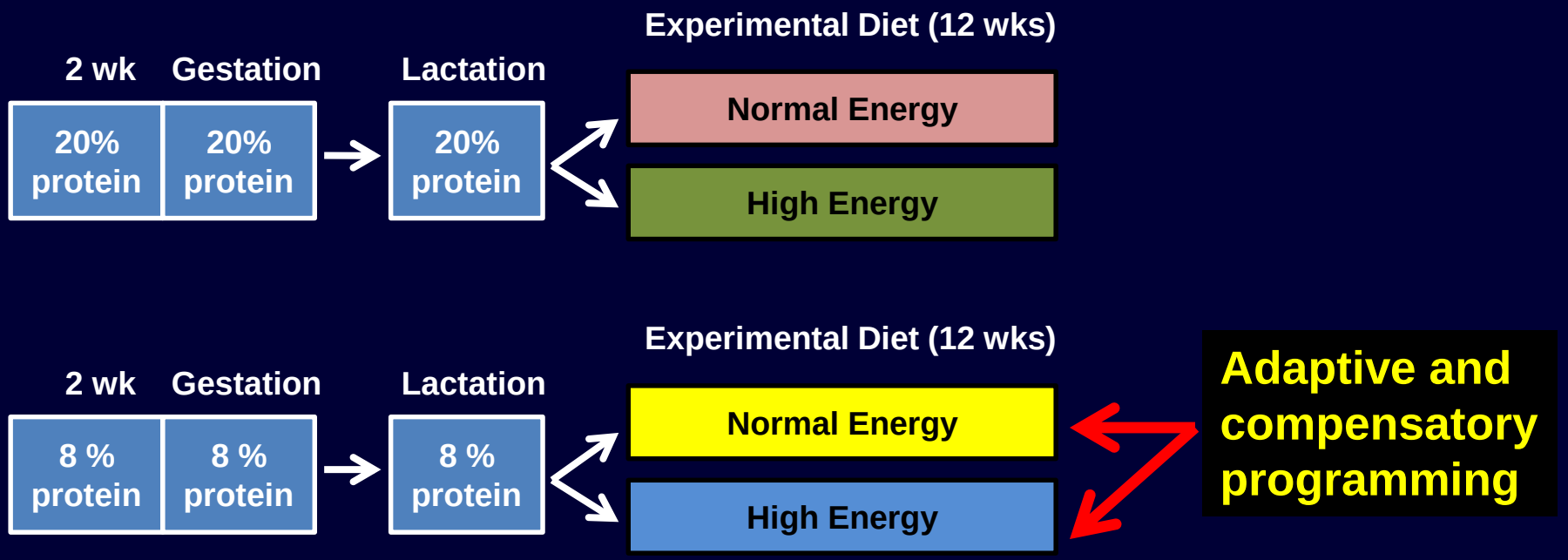
Increased propensity for catch up growth

Epigenetic Programming?

Animal model of obesity and epigenetics

Experimental Design




2 wk
Gestation
Lactation
20% protein
20% protein
20% protein
Experimental Diet (12 wks)
Normal Energy
High Energy
2 wk
Gestation
Lactation
8 % protein
8 % protein
8 % protein
Experimental Diet (12 wks)
Normal Energy
High Energy
Adaptive and compensatory programming

2 wk Gestation

Lactation

Experimental Diet (12 wks)

20% protein

20% protein

20% protein

Normal Energy

High Energy

8 % protein

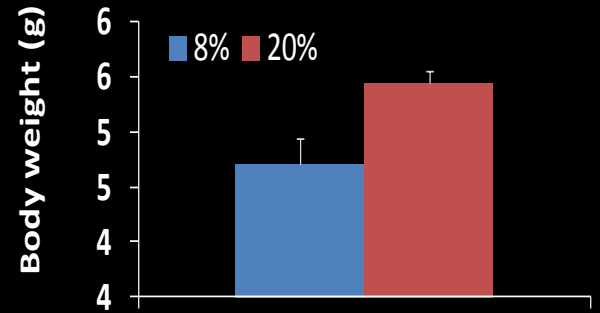
8 % protein

8 % protein

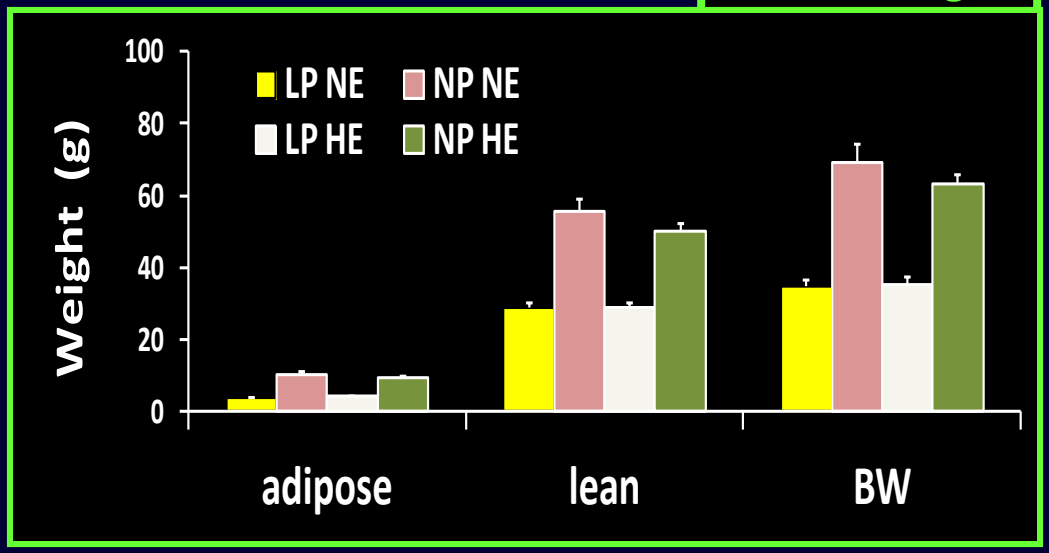
Normal Energy

High Energy

At Birth

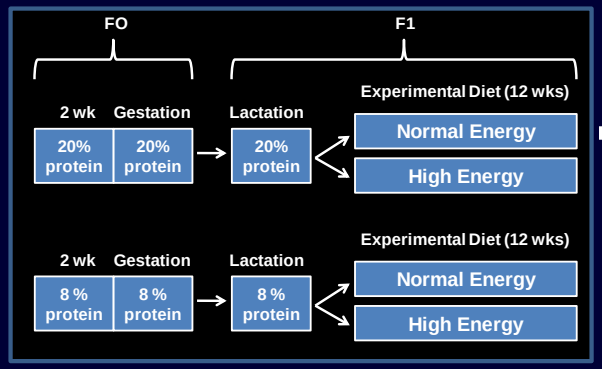


at weaning

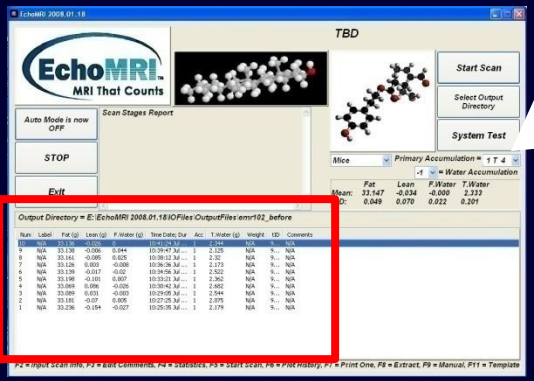


How to measure fat tissue changes over time in live animals?

Magnetic Resonance Imaging (EchoMRI)

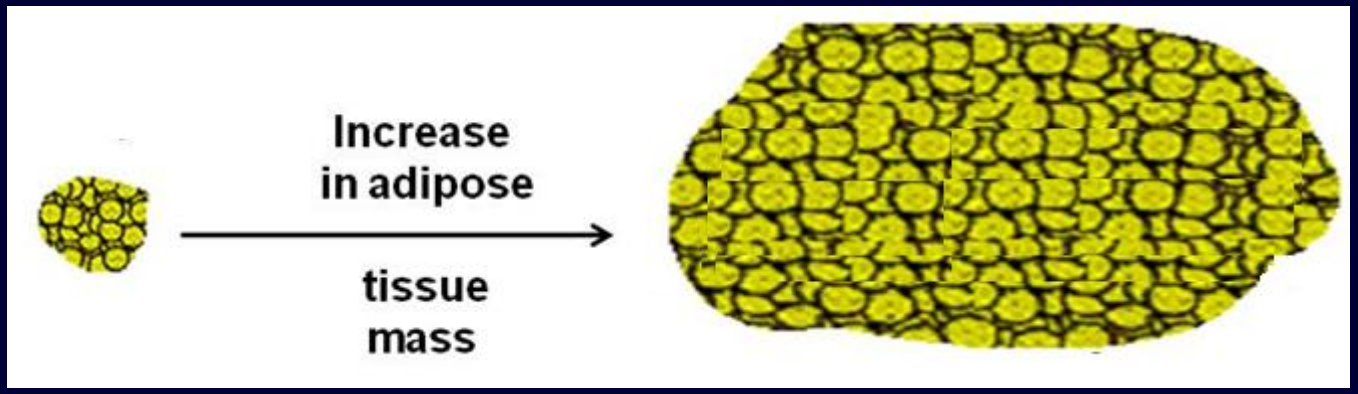


Quantitate fat mass measurement by Echo MRI

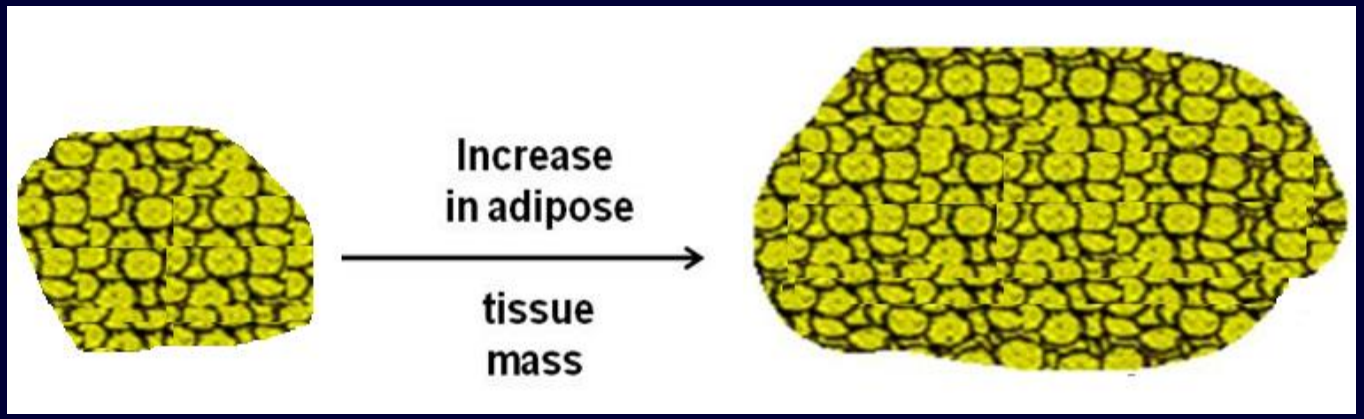


Num	Label	Fat (g)	Lean (g)	F.Water (g)	Time Date; Dur	Acc	T.Water (g)	Weight	tID	Comments
10	N/A	33.136	-0.026	0	10:41:24 Jul ...	1	2.344	N/A	9...	N/A
9	N/A	33.138	-0.006	0.044	10:39:47 Jul ...	1	2.125	N/A	9...	N/A
8	N/A	33.161	-0.085	0.025	10:38:12 Jul ...	1	2.32	N/A	9...	N/A
7	N/A	33.126	0.003	-0.008	10:36:36 Jul ...	1	2.173	N/A	9...	N/A
6	N/A	33.139	-0.017	-0.02	10:34:56 Jul ...	1	2.522	N/A	9...	N/A
5	N/A	33.198	-0.101	0.007	10:33:21 Jul ...	1	2.362	N/A	9...	N/A
4	N/A	33.069	0.086	-0.026	10:30:42 Jul ...	1	2.682	N/A	9...	N/A
3	N/A	33.089	0.031	-0.003	10:29:05 Jul ...	1	2.544	N/A	9...	N/A
2	N/A	33.181	-0.07	0.005	10:27:25 Jul ...	1	2.075	N/A	9...	N/A
1	N/A	33.236	-0.154	-0.027	10:25:35 Jul ...	1	2.179	N/A	9...	N/A

Low Adipose Tissue Weight and Catch-up Growth

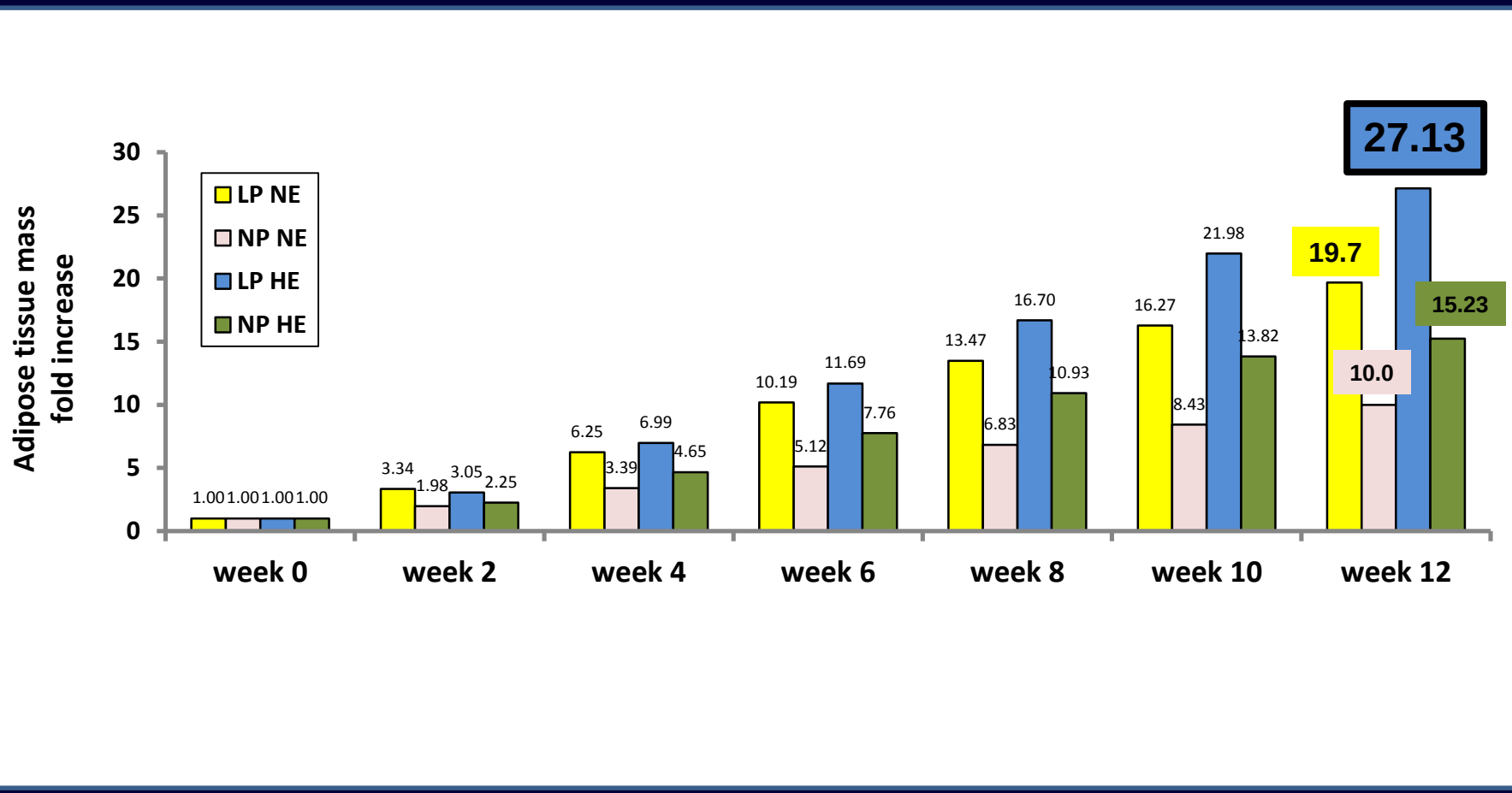


10 fold increase



2.5 fold increase

Adipose tissue mass fold increase



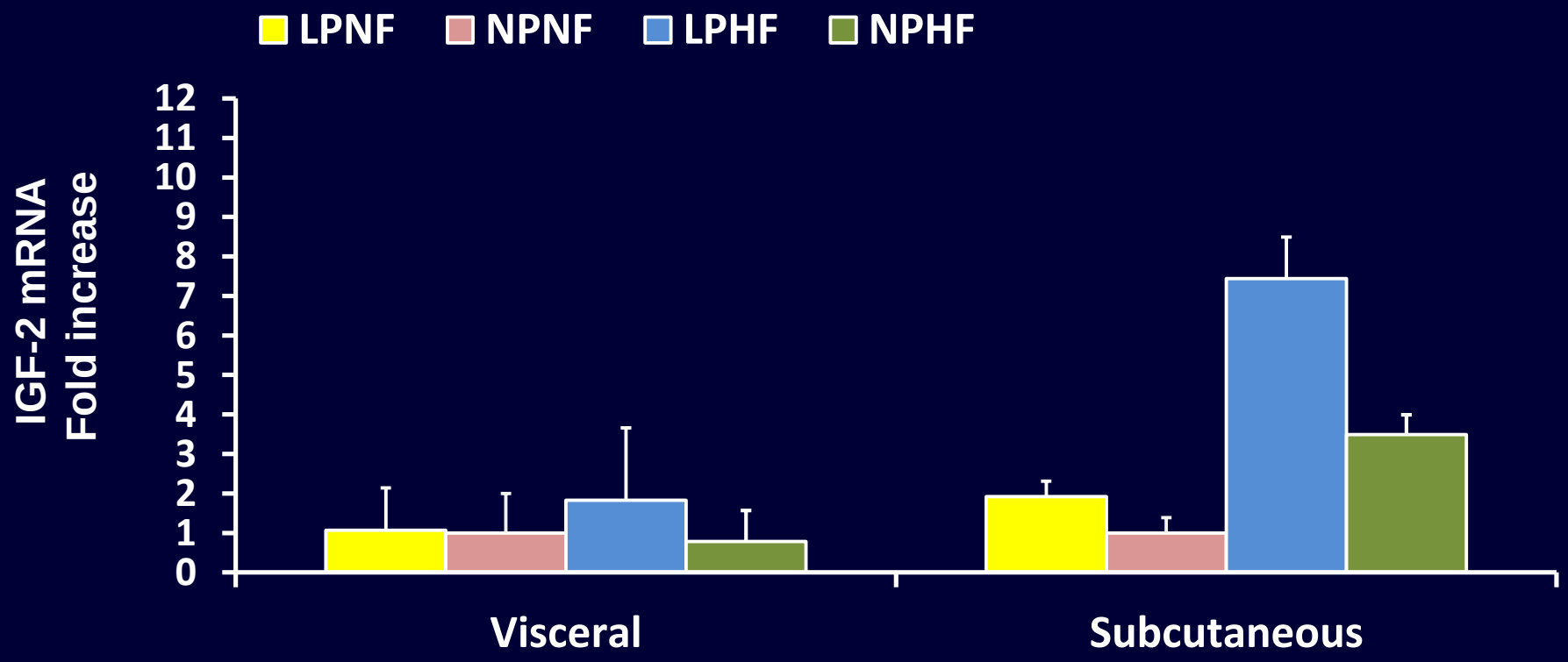
Claycombe et al., accepted, J Nutr. 2013

Effects of prenatal and postnatal diet on imprinted gene expression?

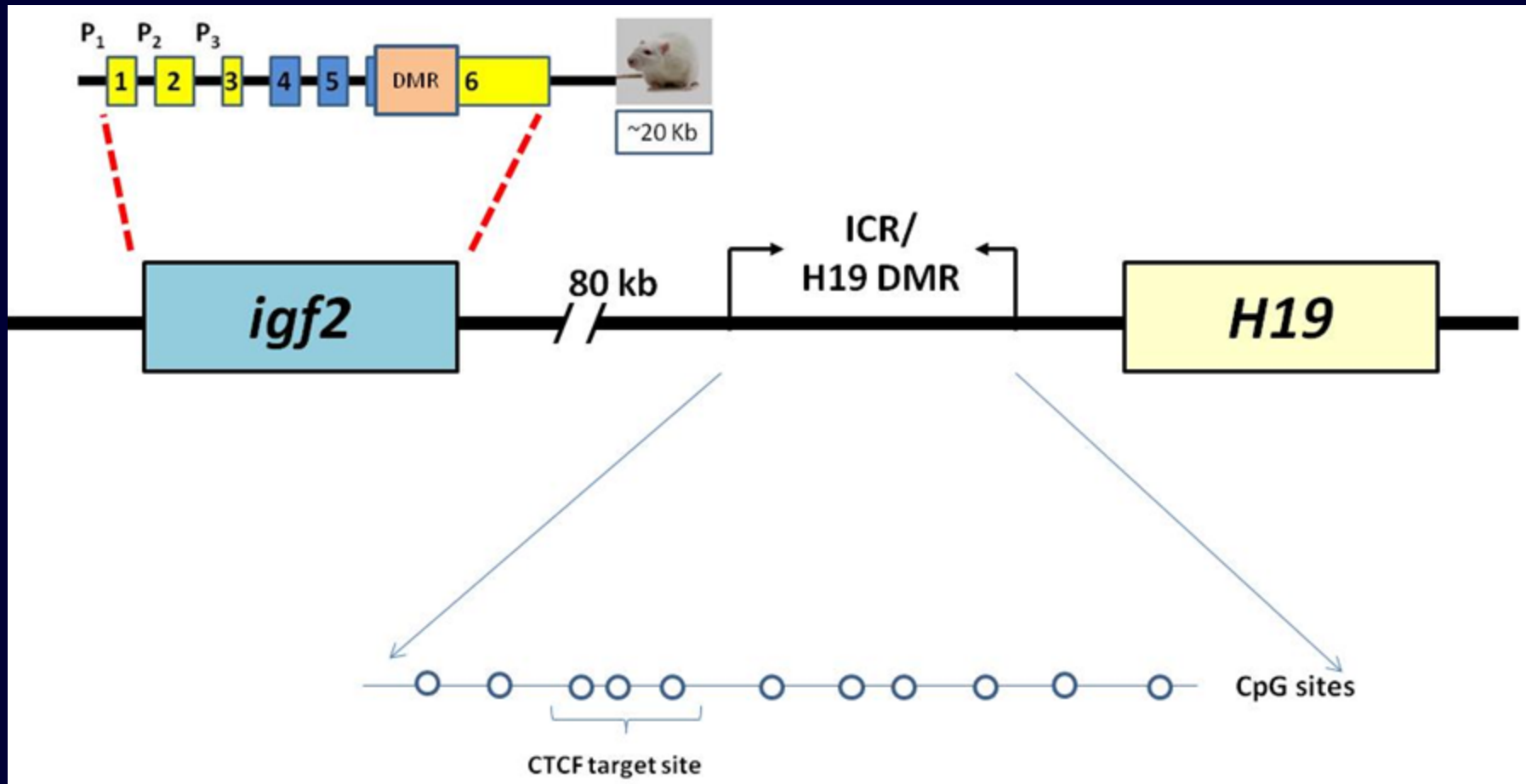
Igf2/H19 Locus

- **Insulin-like growth factor 2 (*IGF2)* was the first imprinted gene identified**
  (*Cell, 64:849-859, 1991)*
- **IGF2 is a major fetal growth factor**
  (*Nature* 417:945-948, 2002)
- **Epigenetics is an inheritable changes that affects gene expression without DNA base pair sequence changes (e.g. DNA methylation, histone modifications)**

Effects of LP prenatal and HF postnatal diet on Adipose Tissue IGF2 mRNA Expression



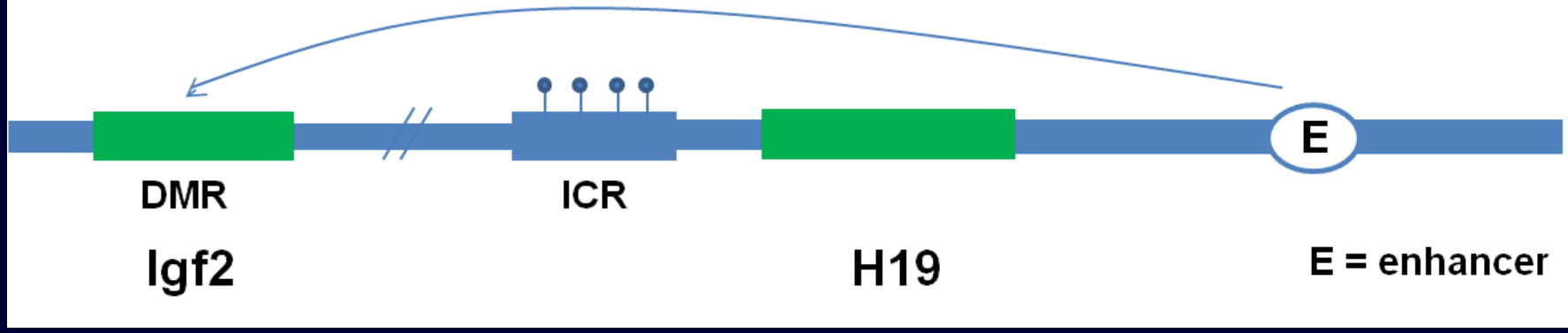
Claycombe et al., J Nutr. 2013

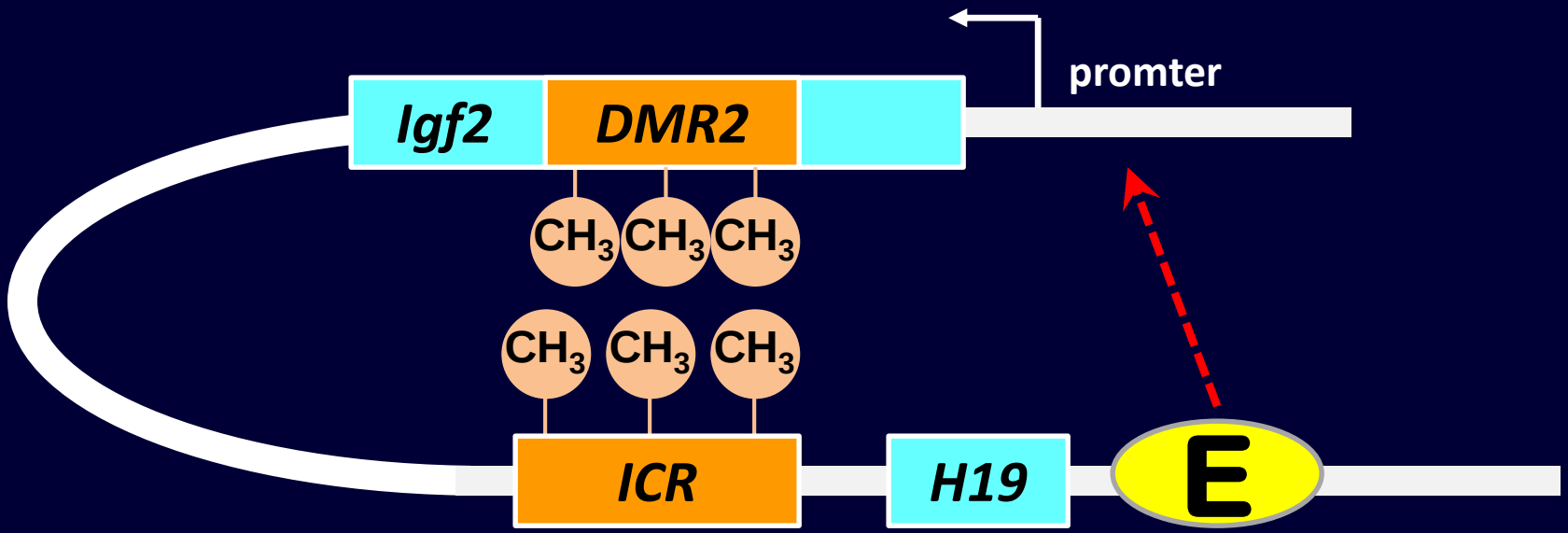


- **CTCF-** CCCTC motif binding factor
- 1-4 CpG sites/CTCF

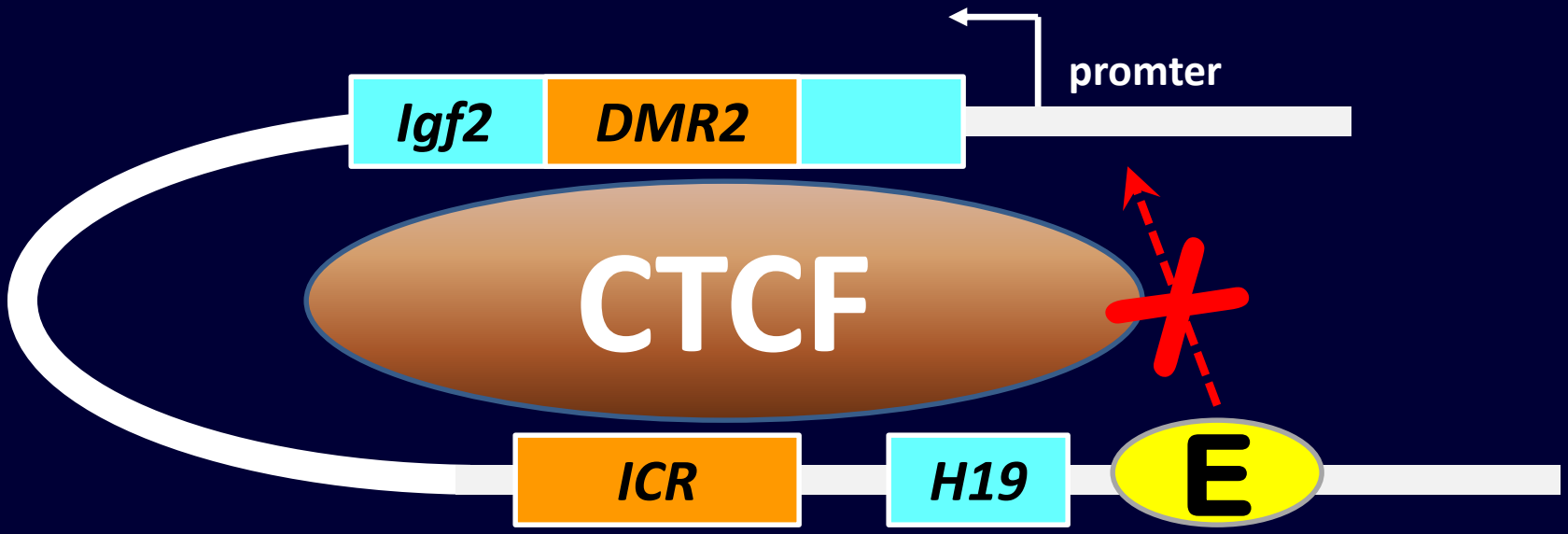
IGF2 transcription activation

NORMALLY: methylation is present in the ICR so there is no CTCF binding and hence Igf2 expression activated.

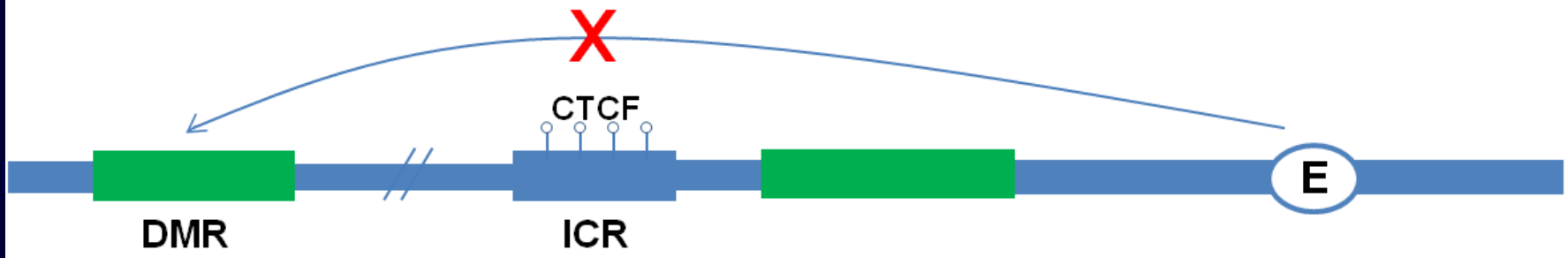




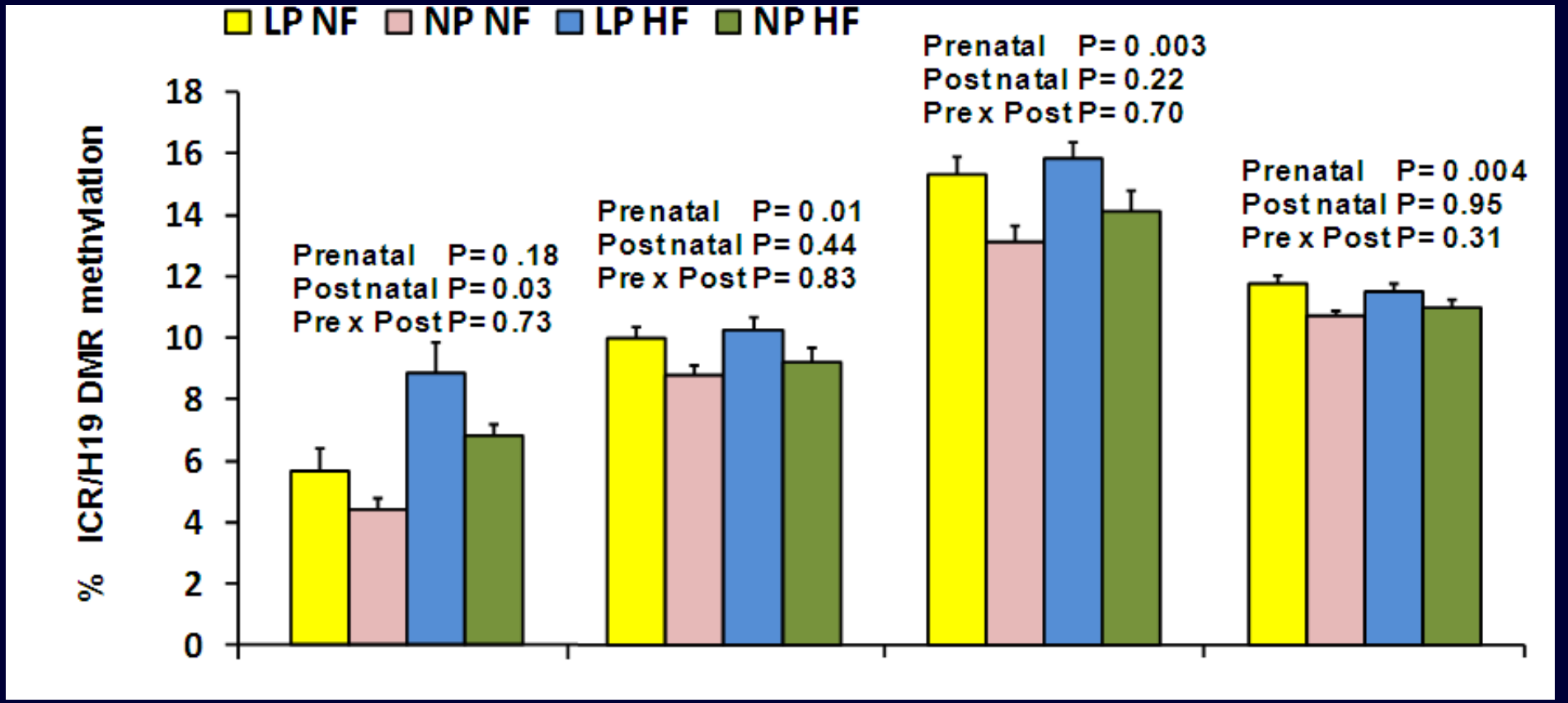
IGF2 transcription repression



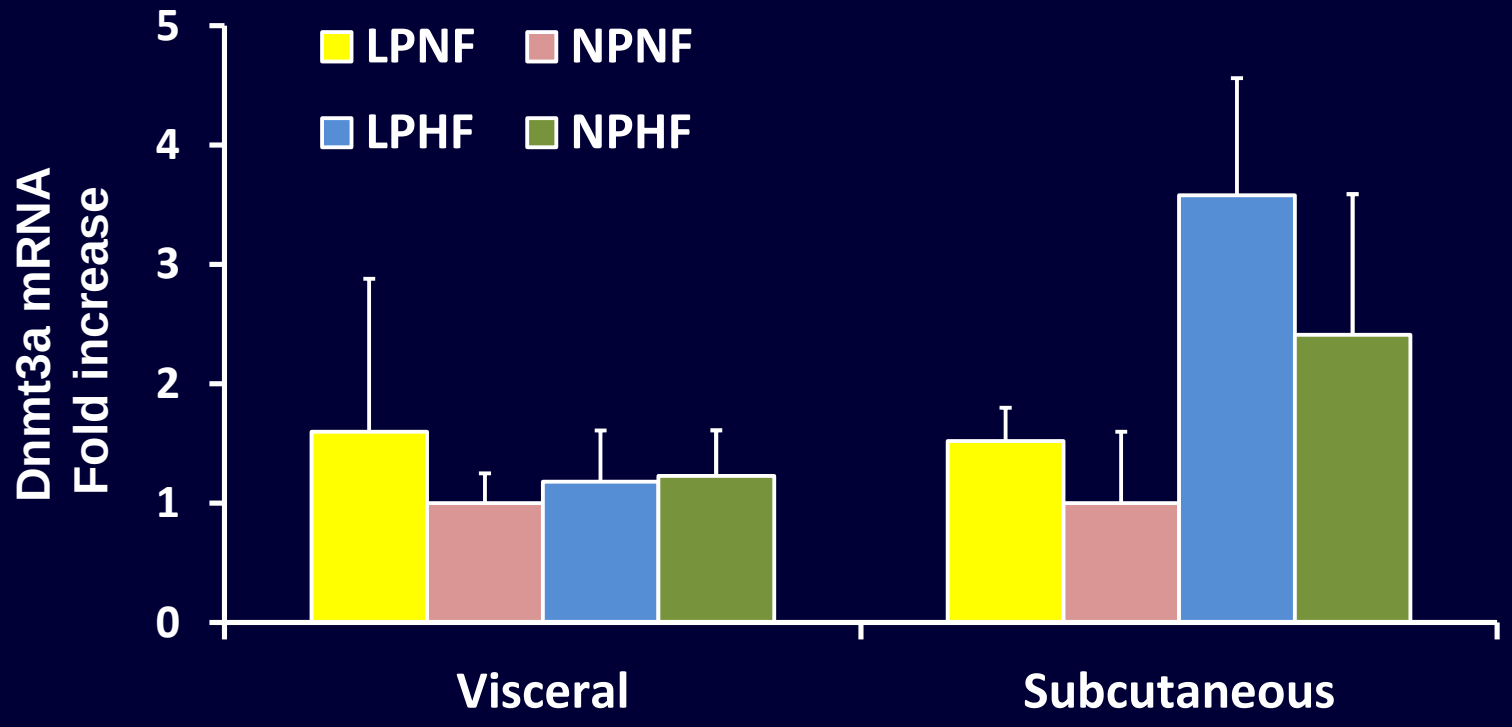
With less methylation or hypomethylation of the ICR there is CTCF binding and Igf2 expression repressed.



ICR/ H19 DMR Methylation in Adipose Tissue

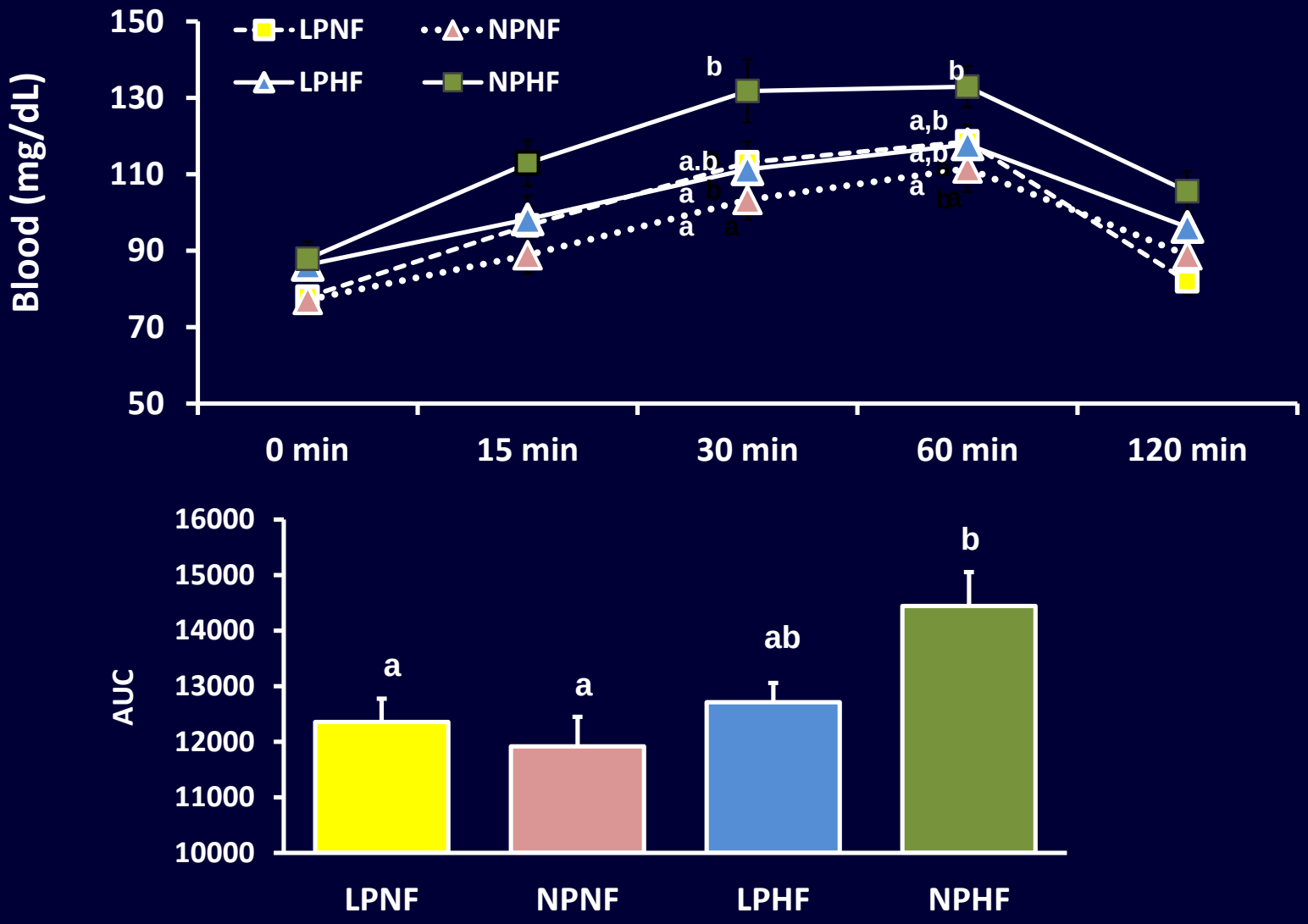


Effects of LP prenatal and HF postnatal diet on Adipose Tissue Dnmt3a mRNA Expression



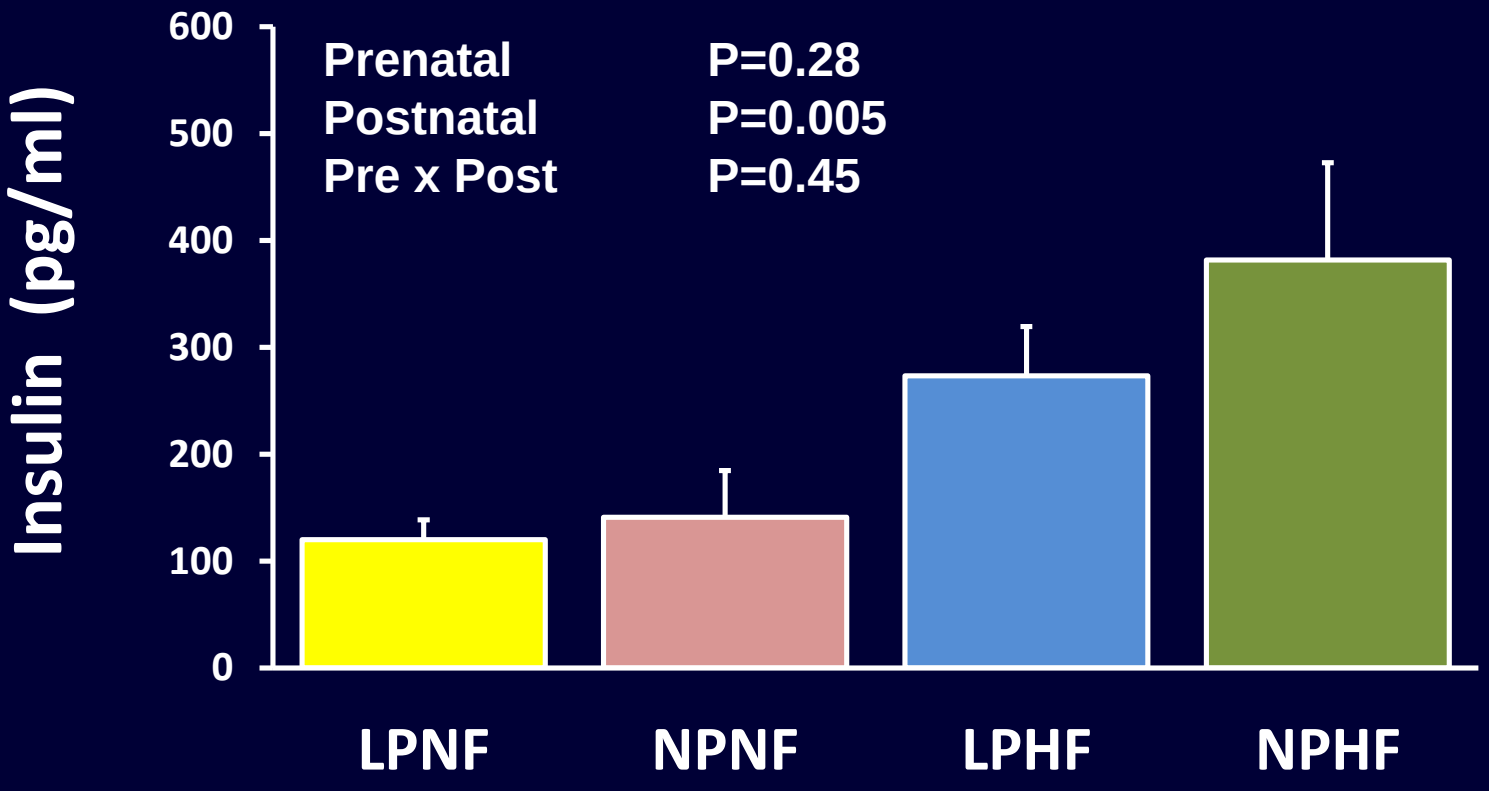
Is there metabolic phenotype associated with catch-up growth?

Effects of LP prenatal and HF postnatal diet on GT



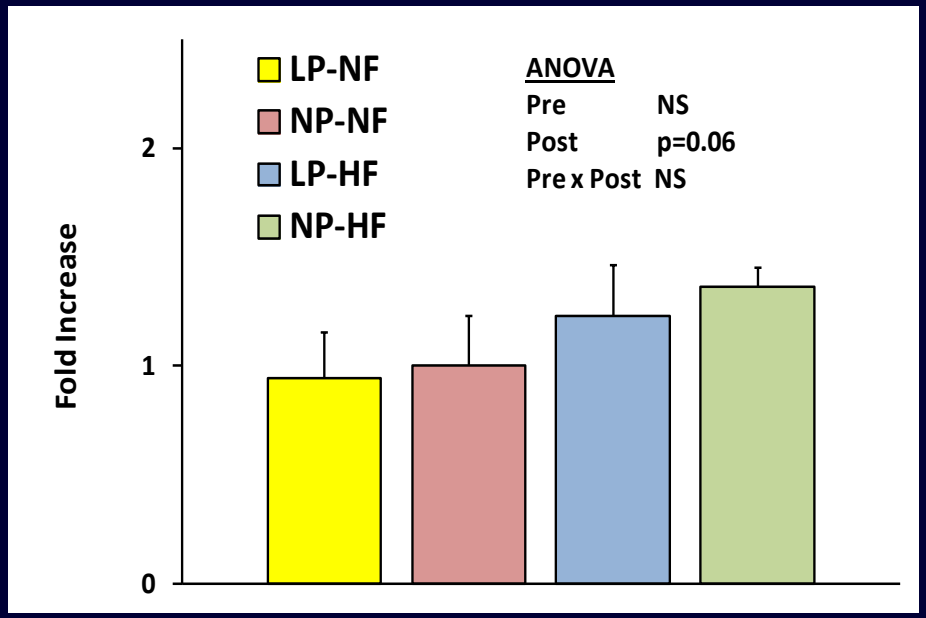
Claycombe et al., J Nutr. 143(10):1533-1539, 2013

Effects of LP prenatal and HF postnatal diet on Plasma Insulin Concentrations

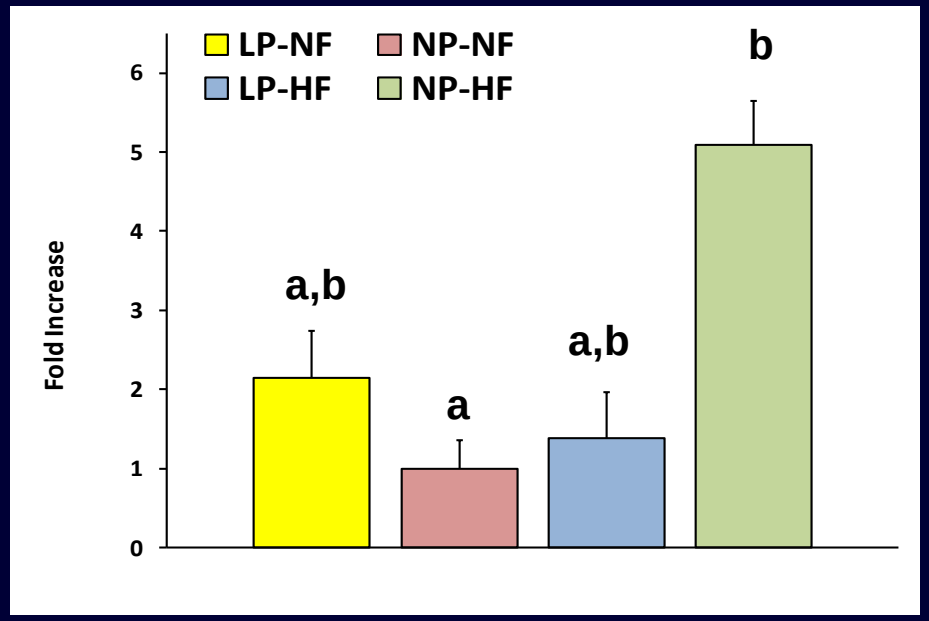


Claycombe et al., J Nutr. 143(10):1533-1539, 2013

Adipose Tissue Mitochondrial Copy Number

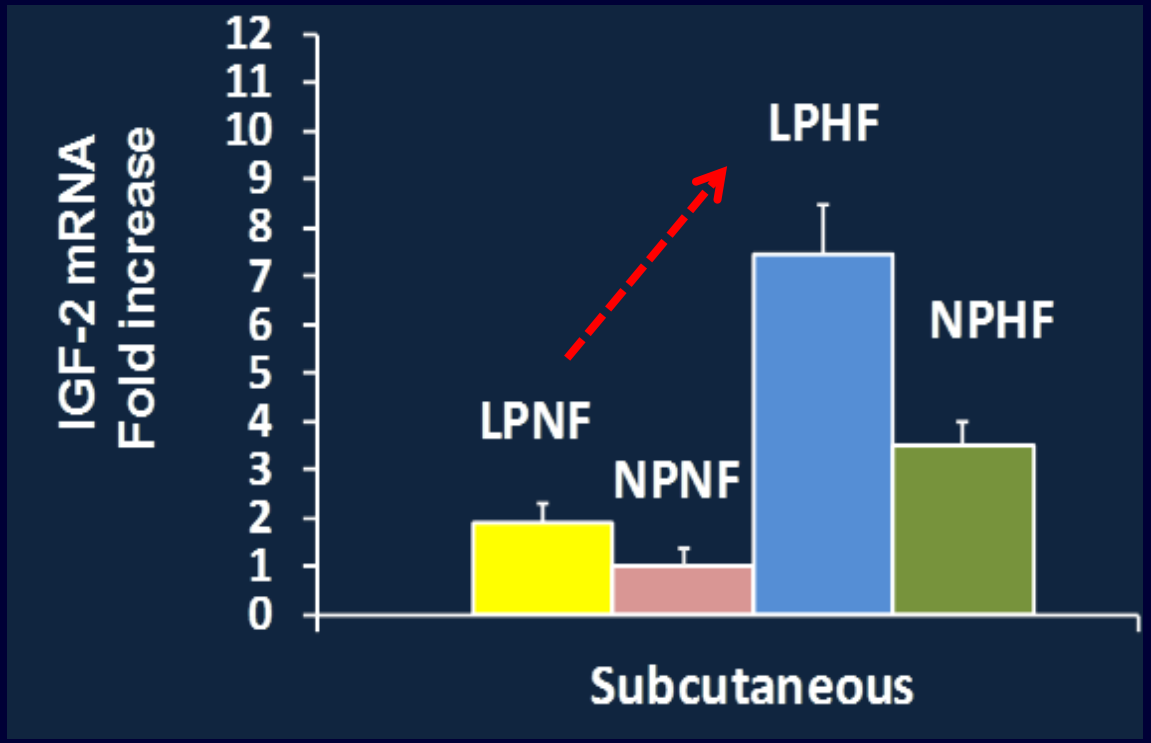


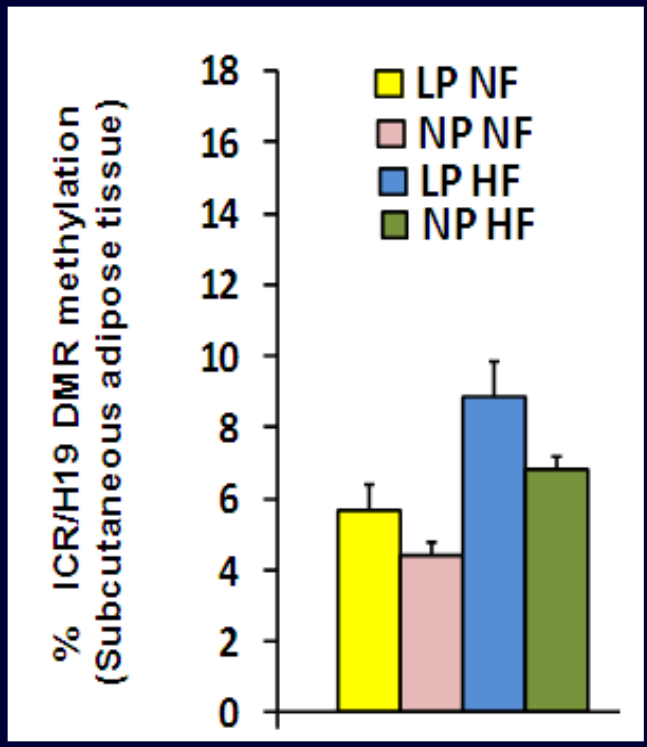
Visceral



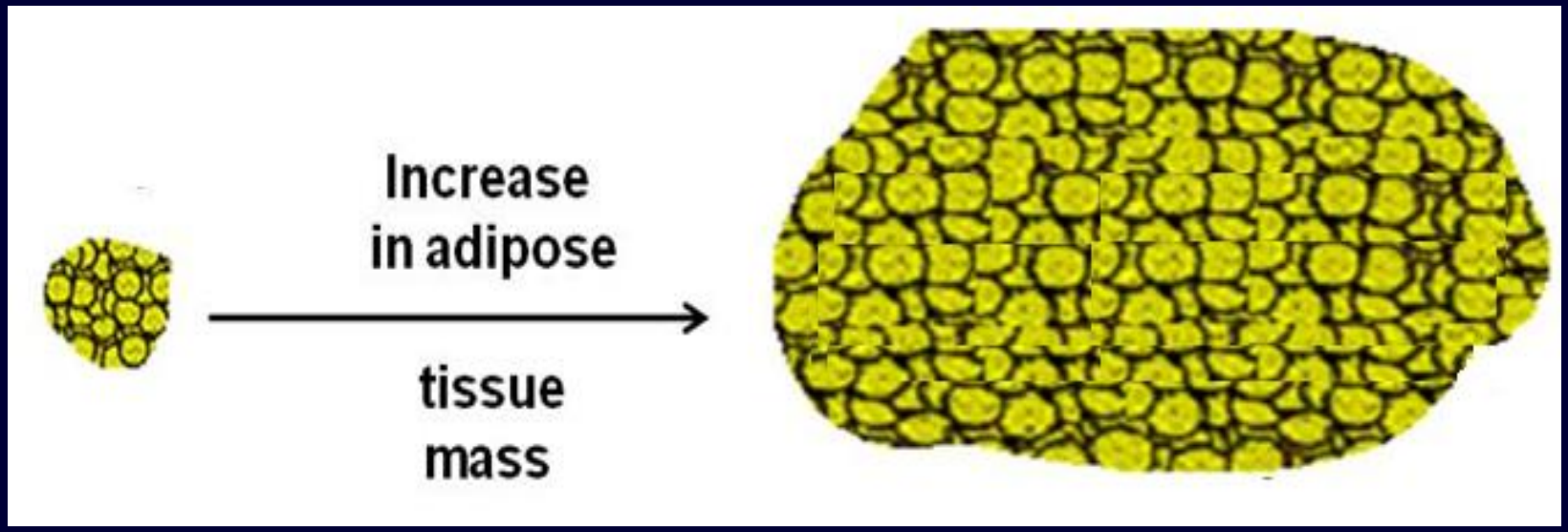
Subcutaneous

Effects of LP prenatal and HF postnatal diet on Adipose Tissue IGF2 mRNA Expression



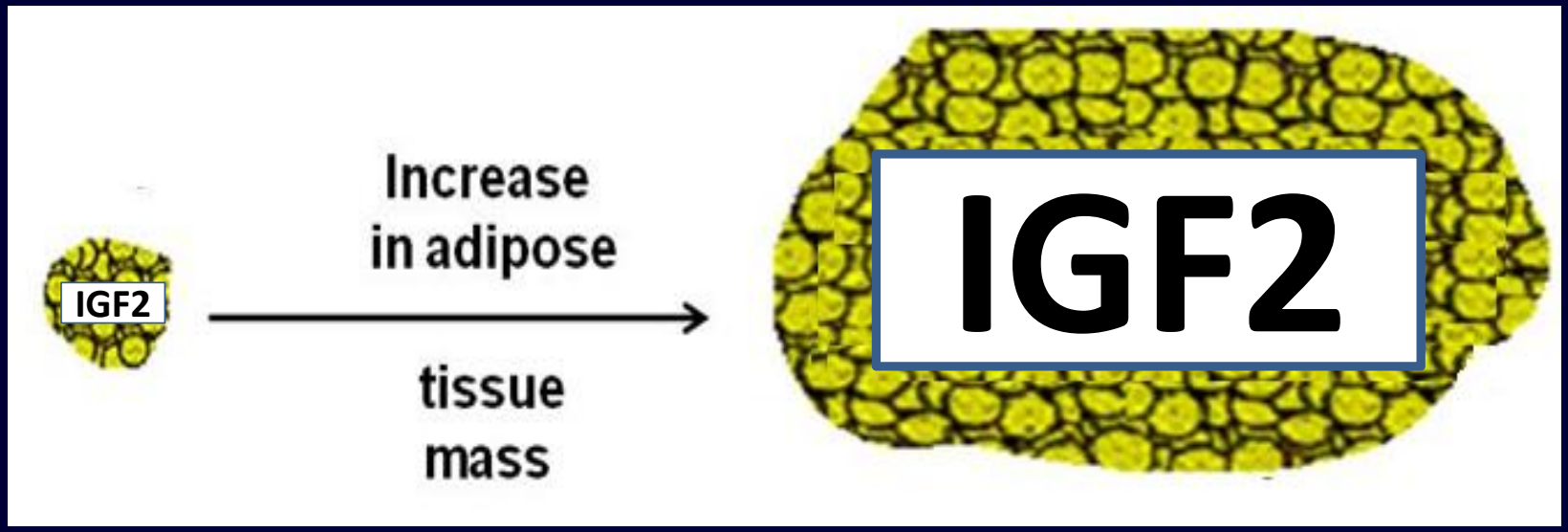


Adipose Tissue Growth and Regulators



Normal **Obesity**

Adipose Tissue Growth and Regulators

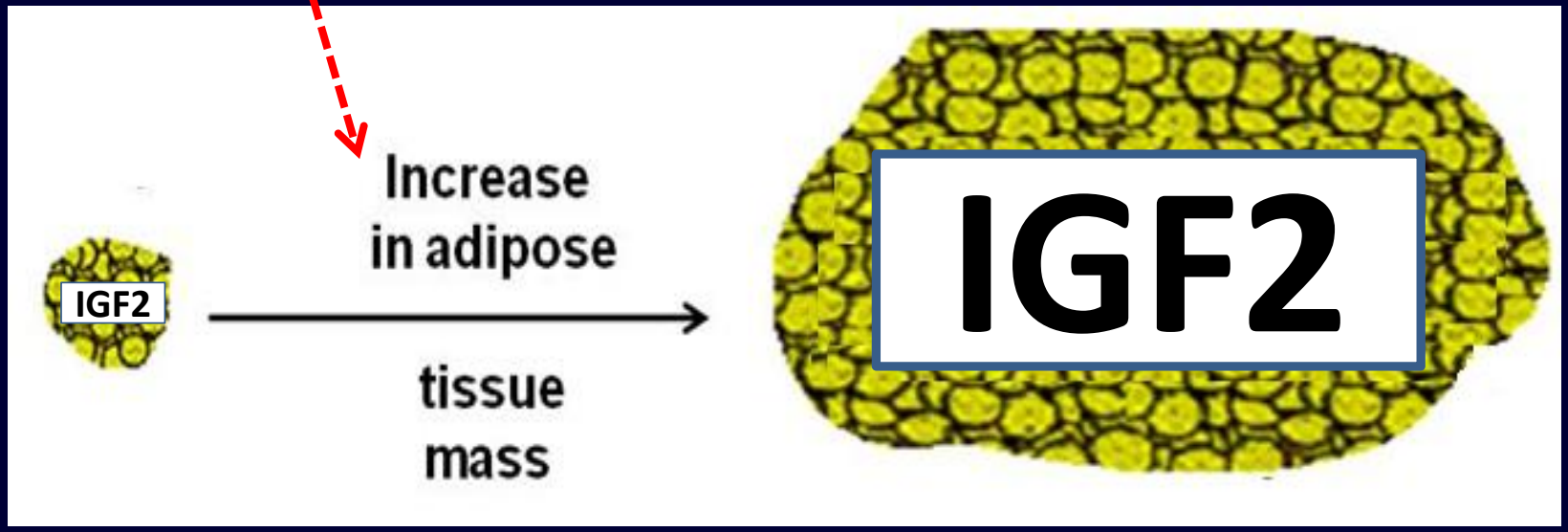


Normal **Obesity**

Adipose Tissue Growth and Regulators

High Fat Diet

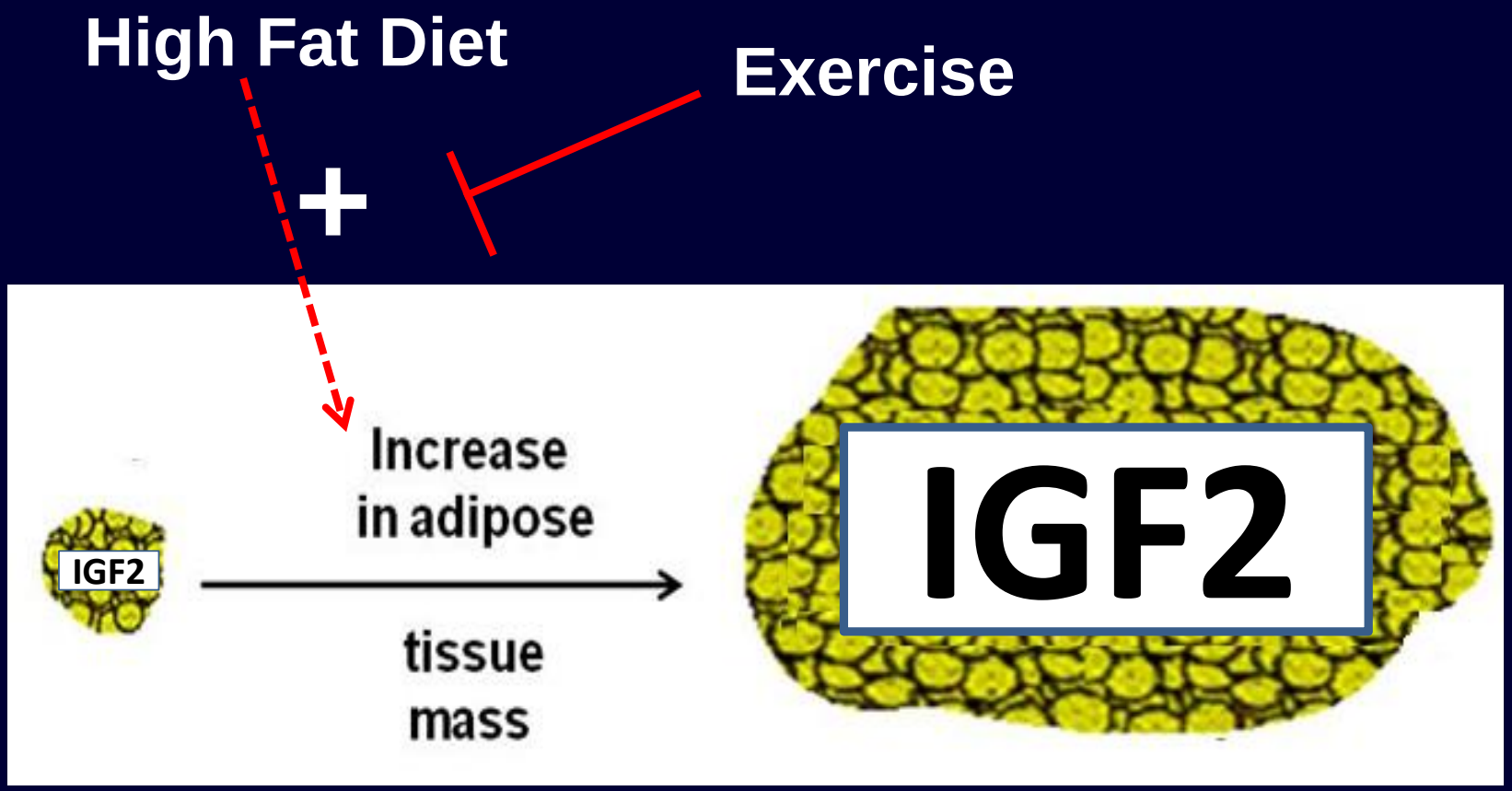
+

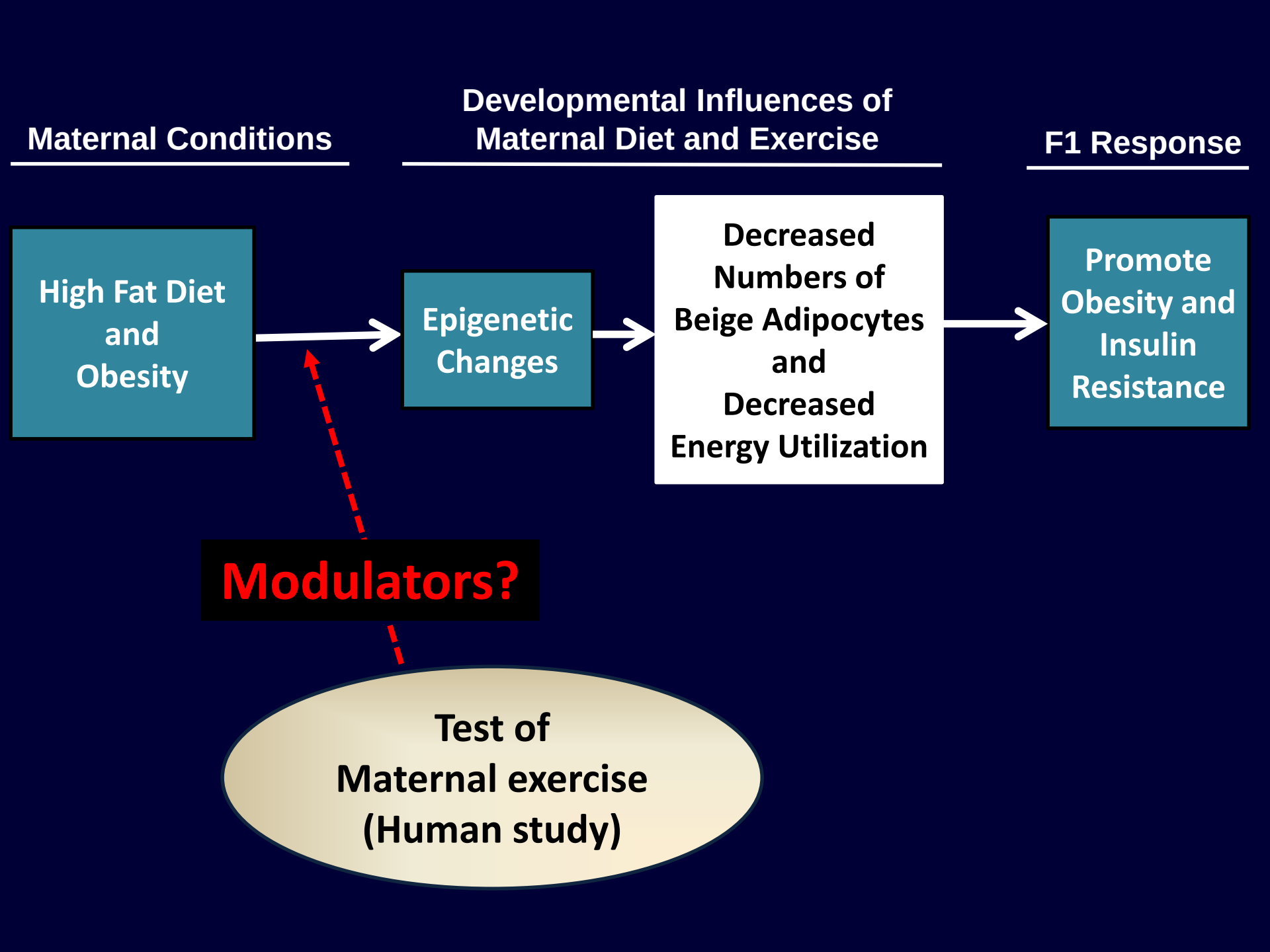


Normal

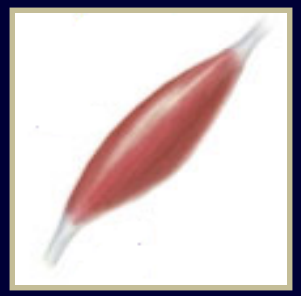
Obesity

Adipose Tissue Growth and Regulators



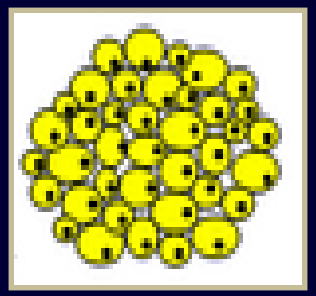

Maternal Conditions
Developmental Influences of Maternal Diet and Exercise
F1 Response
High Fat Diet and Obesity
Epigenetic Changes
Decreased Numbers of Beige Adipocytes and Decreased Energy Utilization
Promote Obesity and Insulin Resistance
Modulators?
Test of Maternal exercise (Human study)

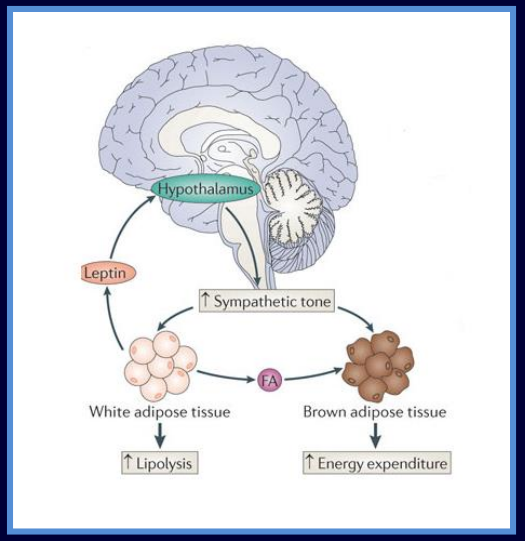
Maternal LP Diet



Endocrine

cross talk





Skeletal muscle

SDH, SIRT3, mt respiration

Adipose tissue

IGF2

Brain and BAT

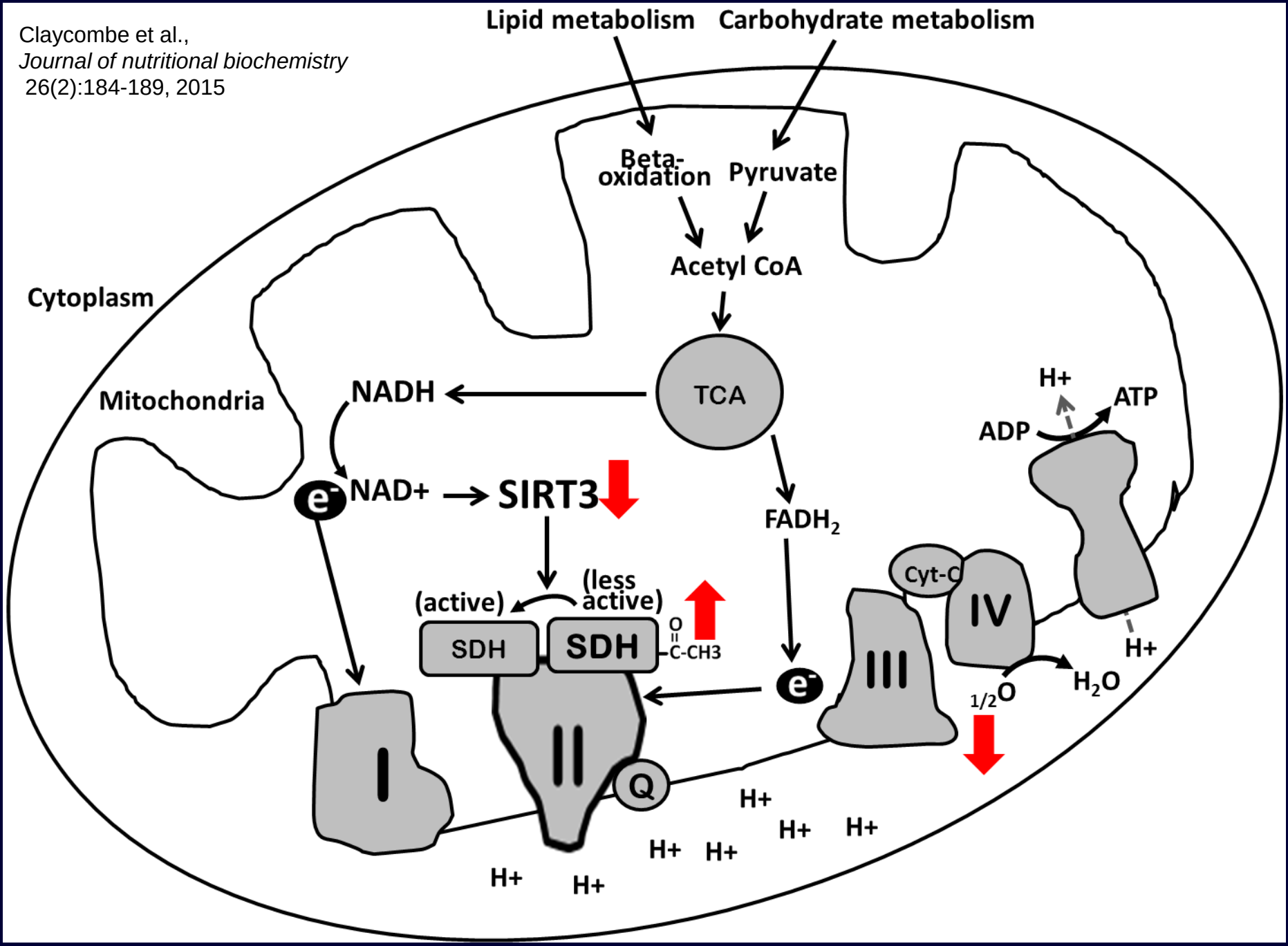
UCP-1, PPAR-a

Insulin Resistance

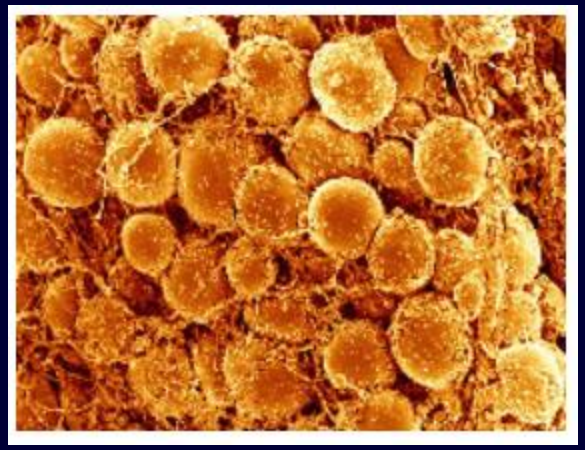
Other metabolic tissues?

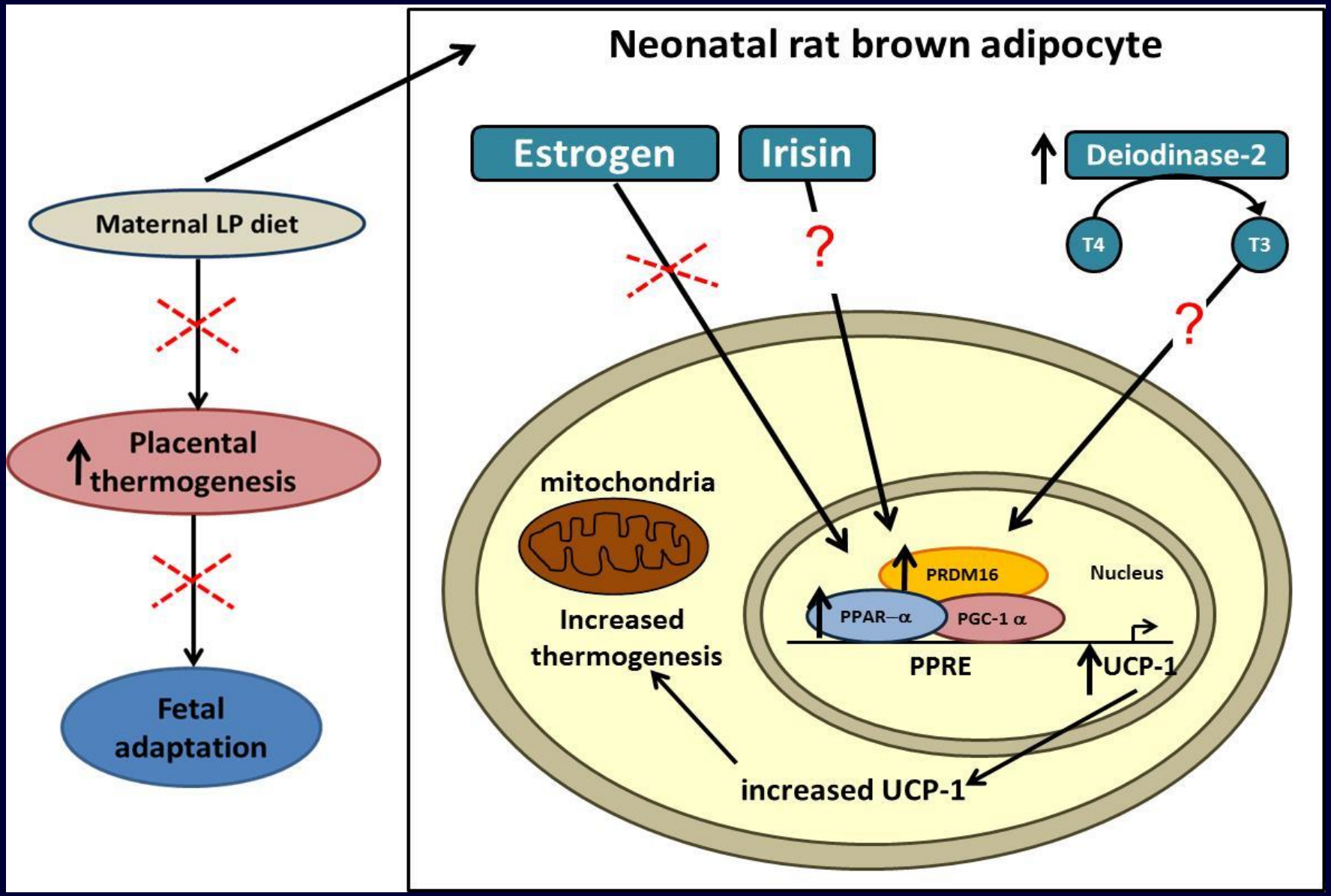
Effects of LP prenatal diet on Muscle Metabolism and mt Function

Claycombe et al.,
Journal of nutritional biochemistry
26(2):184-189, 2015



Effects of LP prenatal diet on Brown adipose tissue function





Claycombe et al., Journal of Nutritional Biochemistry 26(7):729-735, 2015

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Thank you