8th International Research Conference on Adolescents and Adults with FASD

Prenatal alcohol exposure and metabolic disease in adulthood

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CARDD
Collaboration for Alcohol Related Developmental Disorders

The University Of Queensland AUSTRALIA | Faculty of Medicine

Acknowledgments

Alcohol project

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Learning Objectives:

- What is ‘fetal/developmental’ programming” and is there a role for prenatal alcohol exposure?
- Explore the long term consequences for metabolic, health (and disease) following prenatal alcohol exposure
  - Effects on males and females may be different
  - Timing and dose of prenatal exposure is important
- Mechanisms causing ‘programming’ in the peri-conceptional period
  - circadian rhythm changes
  - Epigenetic changes

The DOHaD hypothesis

- Developmental Origins of Health and Disease
  - Developed from ‘Barker Hypothesis’
  - Dutch Famine Studies
    - Concept of critical windows
    - Strong programming of metabolic outcomes

DOHaD in human populations: Dutch Winter Famine

First trimester

- Glucose intolerance
- Cardiovascular disease
- Hypertension
- Dyslipidemia
- Obesity
- Affective disorders

Second trimester

- Glucose intolerance
- Pulmonary disease
- Renal disease

Third trimester

- Glucose intolerance

Programming of Metabolic syndrome

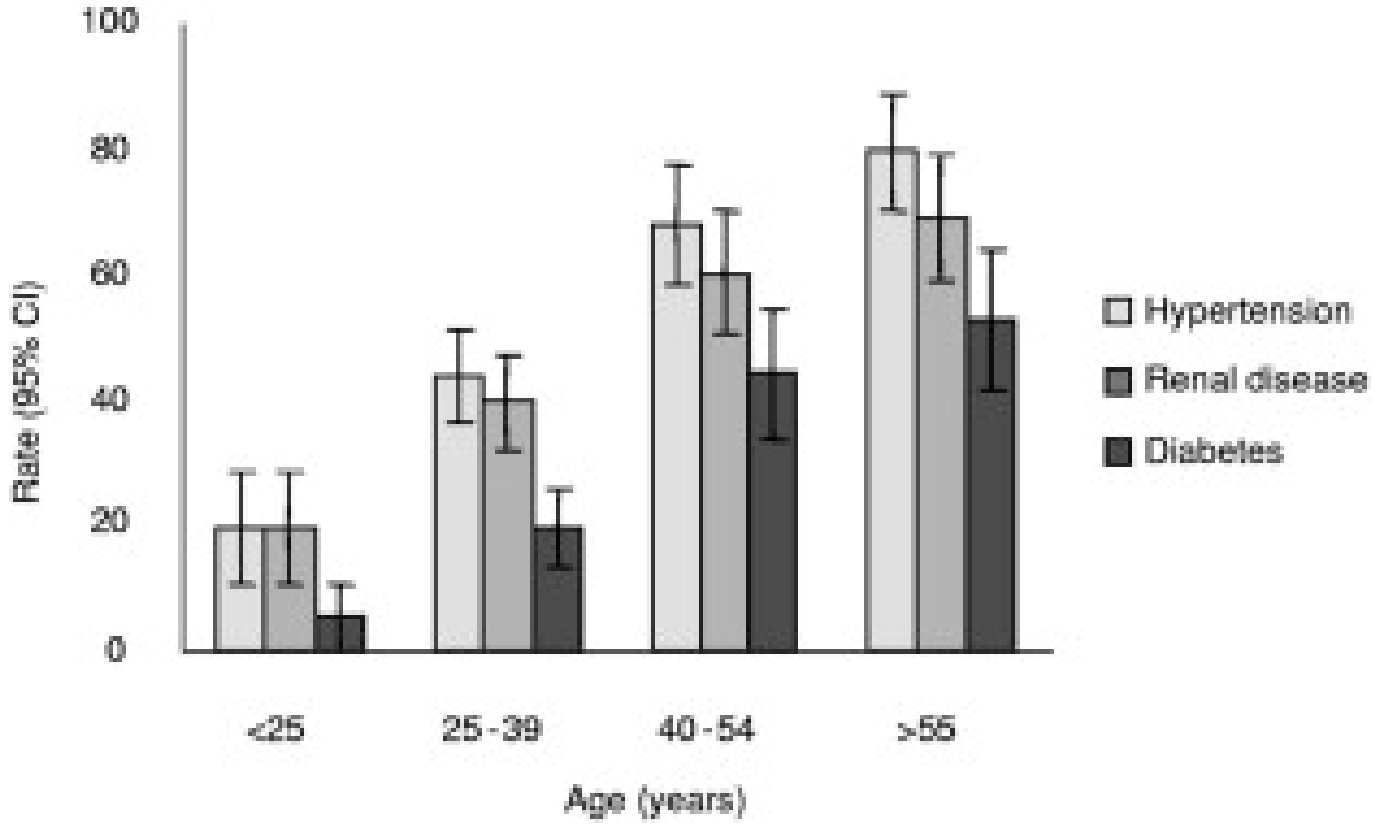
Birthweight (kg)	Total no.	No. with Syndrome X	Odds ratio (95% CI)
≤ 2.5	20	6	18 (2.6 -118)
-2.95	54	10	8.4 (1.5 -49)
-3.41	114	19	8.5 (1.5 - 46)
-3.86	123	15	4.9 (0.9 - 27)
-4.31	64	4	2.2 (0.3 - 14)
>4.31	32	2	1.0

Low birth weight adults (<2.95 kg) have a 10-fold increased risk of developing Syndrome X, whereas lifestyle factors (smoking, overeating), increased the risk up to 3-fold.

Barker et al. (1993) Diabetologia 36:62-67

Why study prenatal alcohol in the context of DOHaD?

Australian Aborigines and programming



Prevalence of morbidities in one remote community in Australia.

Hoy et al, American Journal of Kidney Diseases Volume 56, 2010, 983 - 993

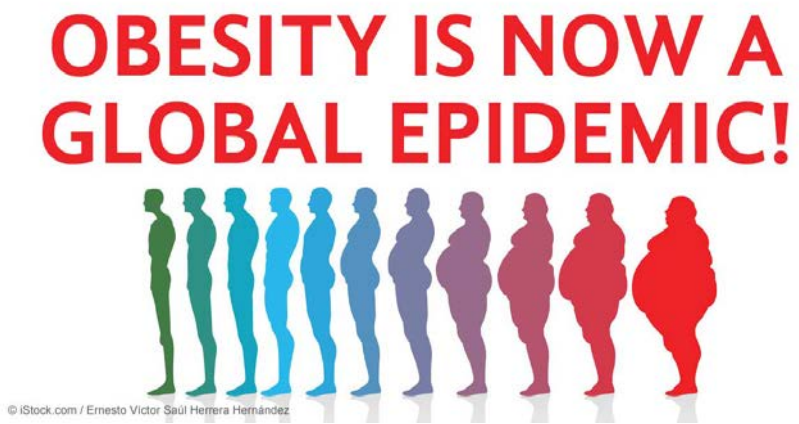
Animal models for fetal alcohol exposure

- Chronic, low/moderate (daily consumption)
  - Liquid diet containing 6% v/v ethanol, consumed *ad lib*
  - BAC- ~0.03-0.04%

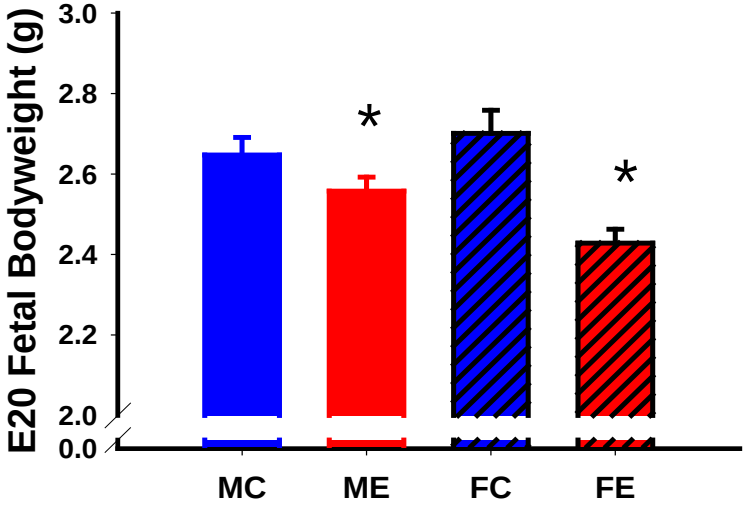
- Periconceptional exposure (E-4 until E4)
  - Liquid diet containing 12% ethanol consumed *ad lib*
  - Second hit – high fat diet from 3 months of age

What metabolic outcomes can be programmed by prenatal alcohol exposure?

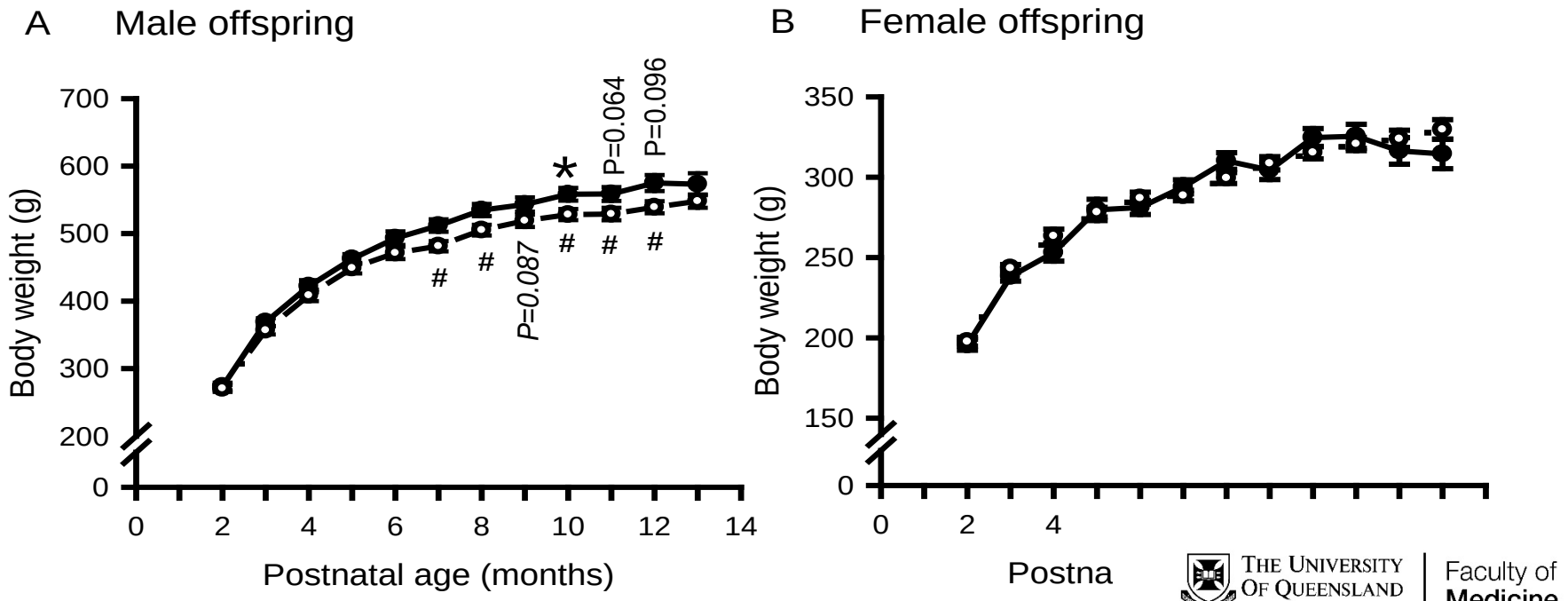
- Fetal and offspring growth
- Metabolic outcomes
  - Basal blood glucose
  - Glucose tolerance test and insulin challenge
  - Food preference
  - Interaction with a lifestyle factor (high fat diet)
  - Hyperlipidemia? Fatty liver?



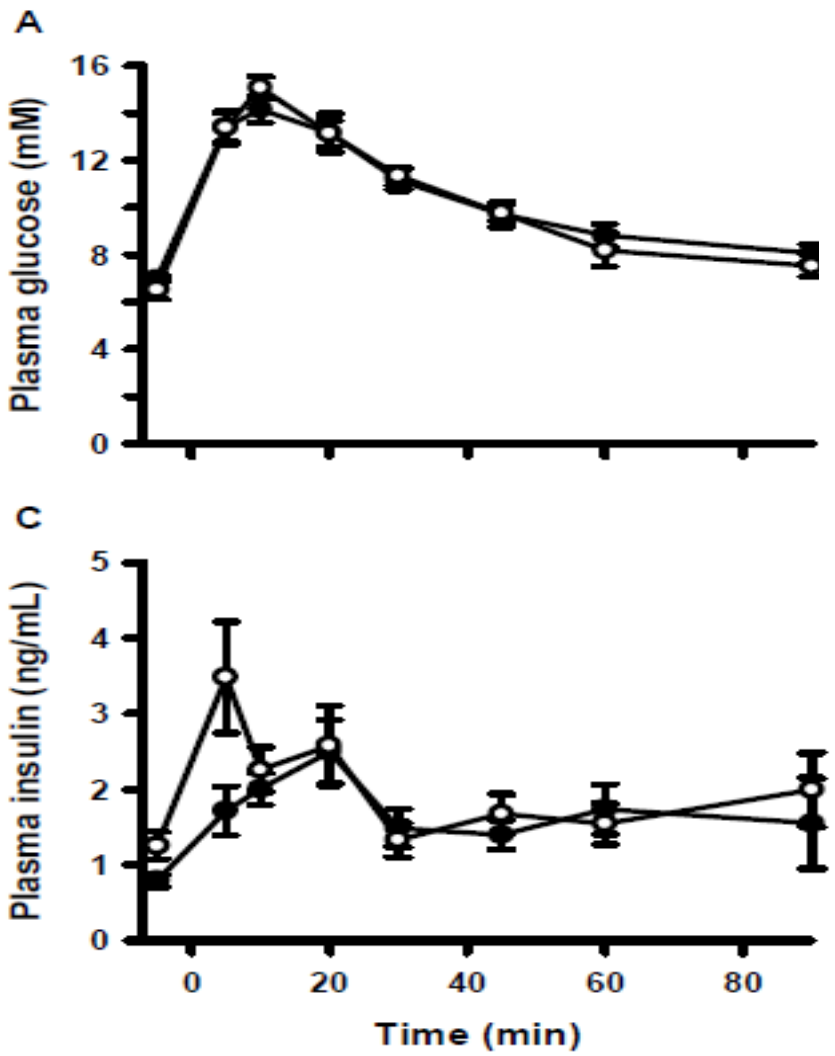
Prenatal alcohol and fetal growth (1)

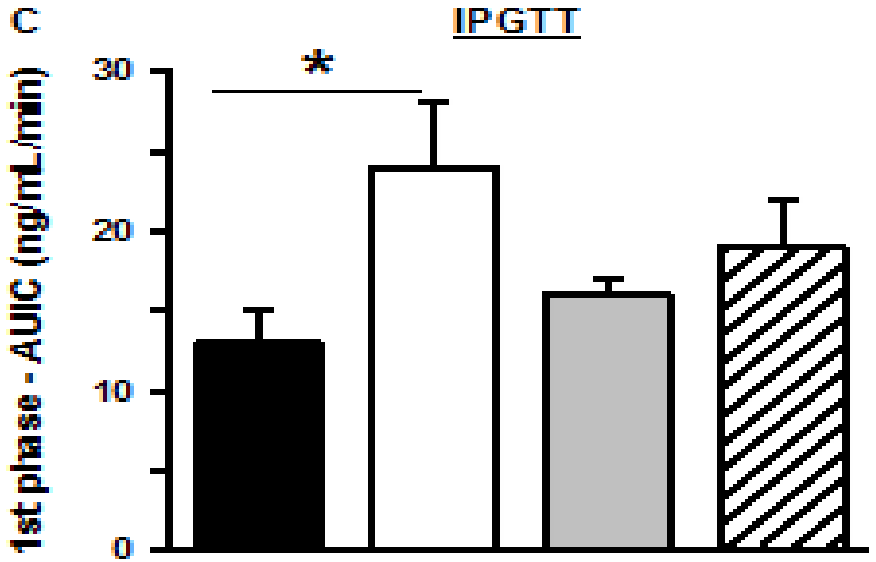


CLD: Low Birth Weight
Catch up growth during weaning,
Males have slowed growth in later life



Prenatal alcohol and metabolic outcomes – Glucose homeostasis



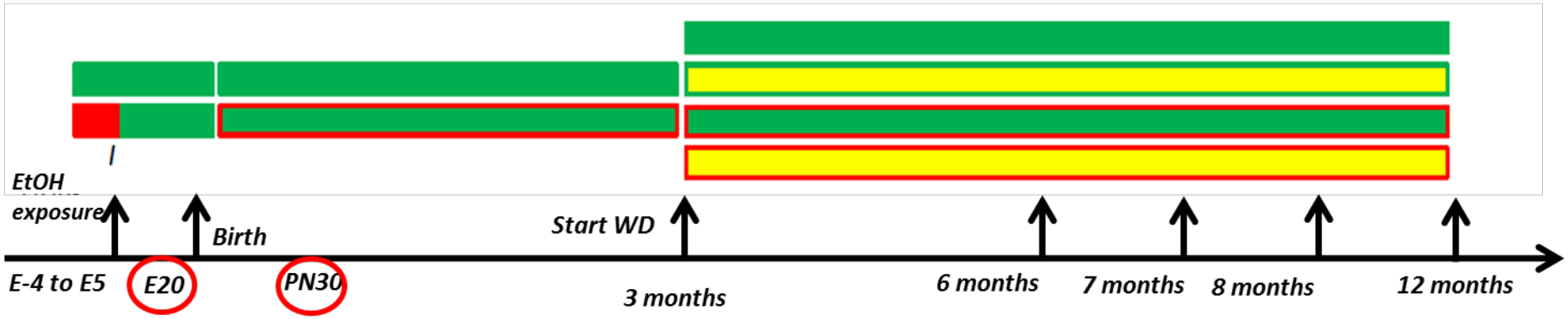


Normal basal blood glucose
Elevated basal insulin
Elevated 1st phase insulin secretion
ONLY in males

Probyn et al, PLoS One, 2013

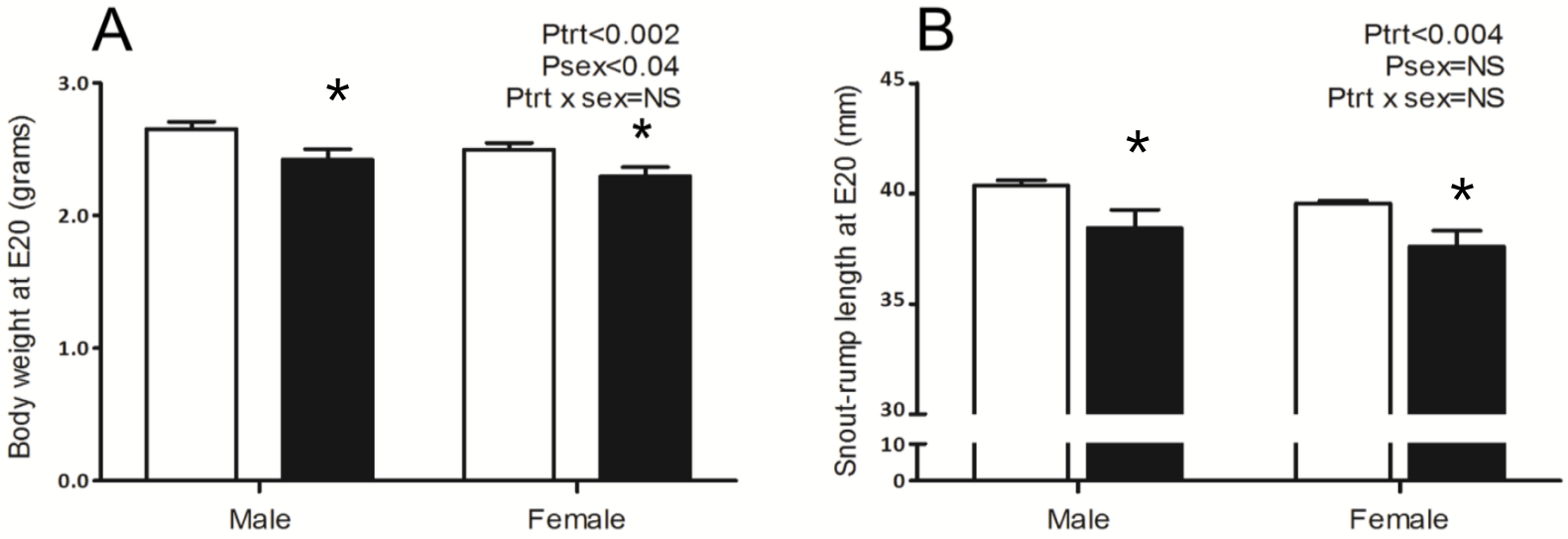
What about exposure only around the time of conception?

Periconceptional alcohol exposure: - interaction with a postnatal high fat diet



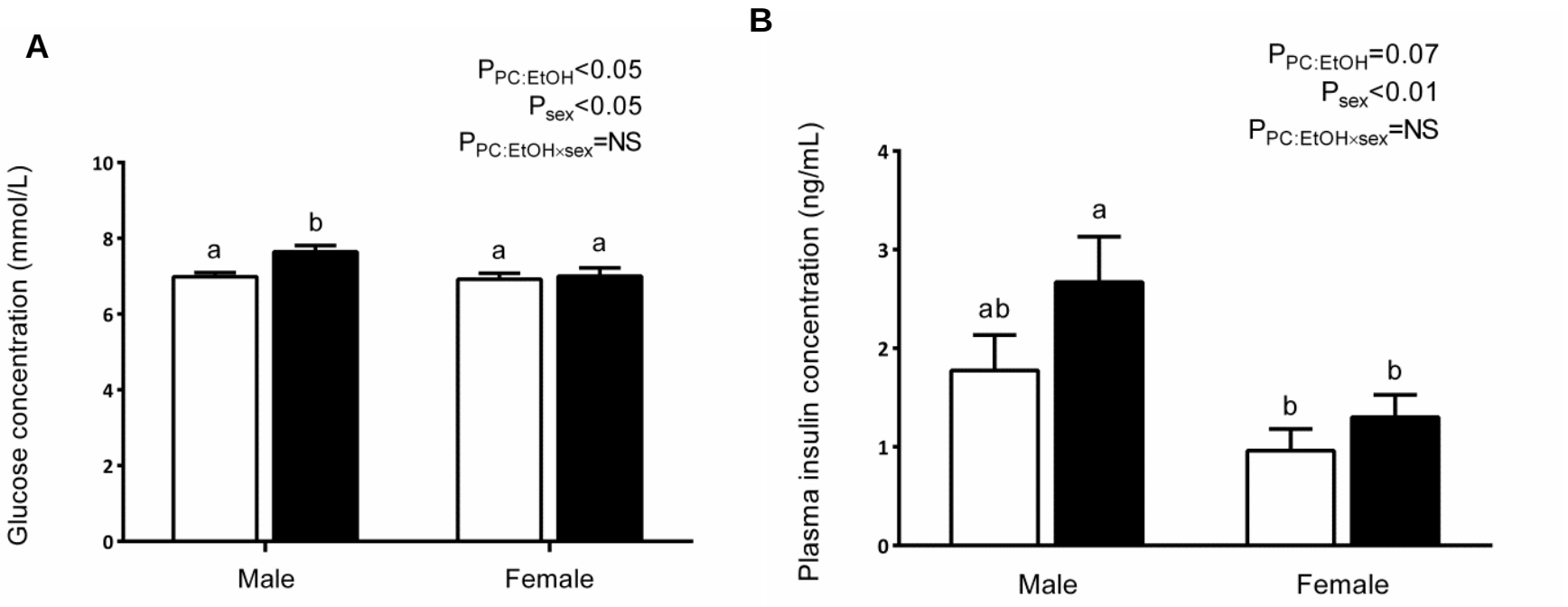
Fetal growth
Placenta

Prenatal alcohol and fetal growth (2)



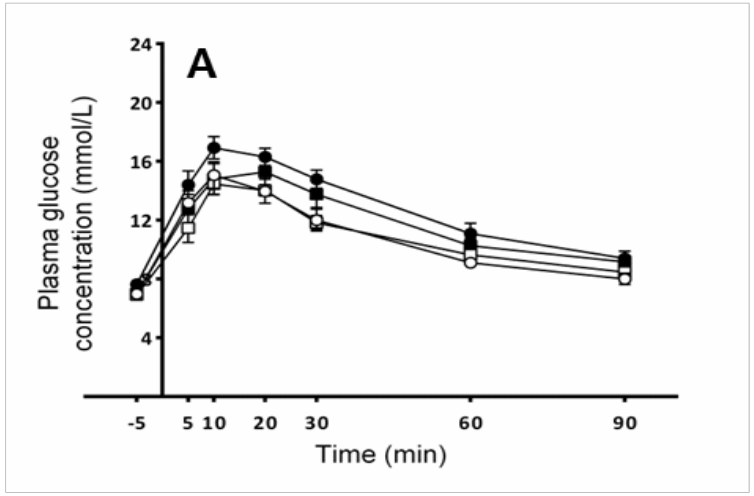
PCE: Reduced fetal weight & body length in late gestation,
Catch up growth during weaning
Normal body weight in adulthood

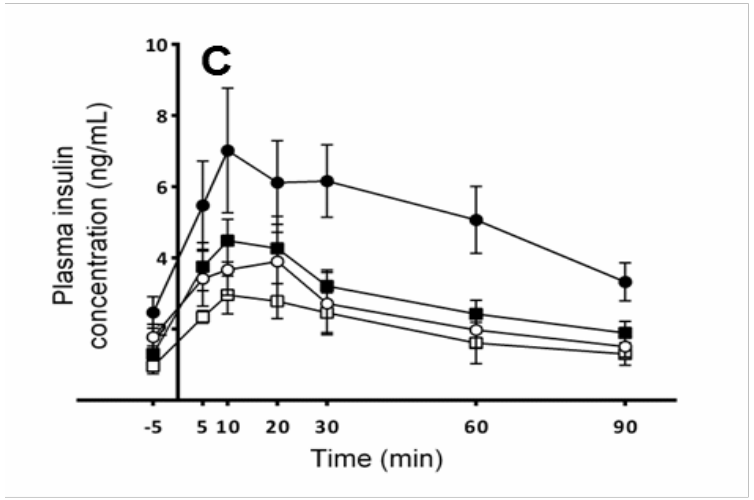
PCE causes elevations in fasting glucose and insulin in males at 8 months

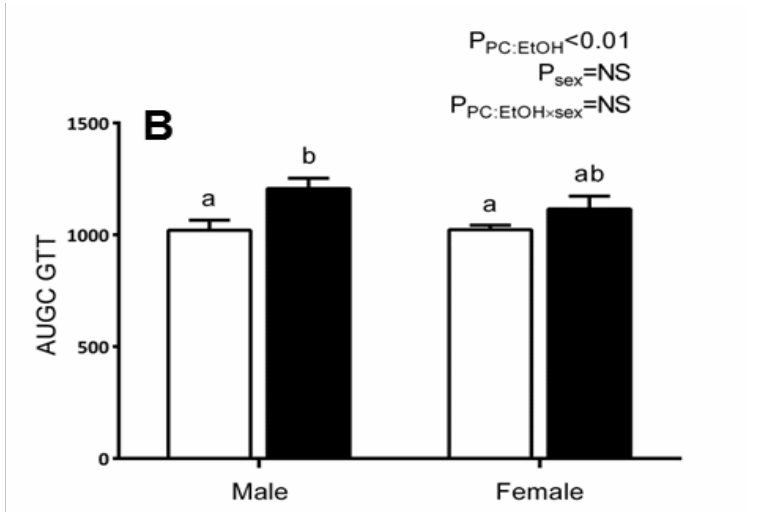


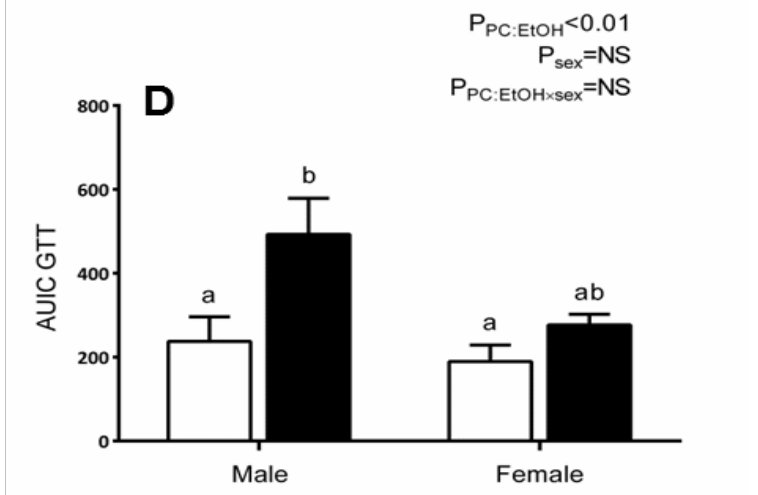
Gardebjer et al, FASEB J. 2015 Jul;29(7):2690-701

PCE: Response to a GTT



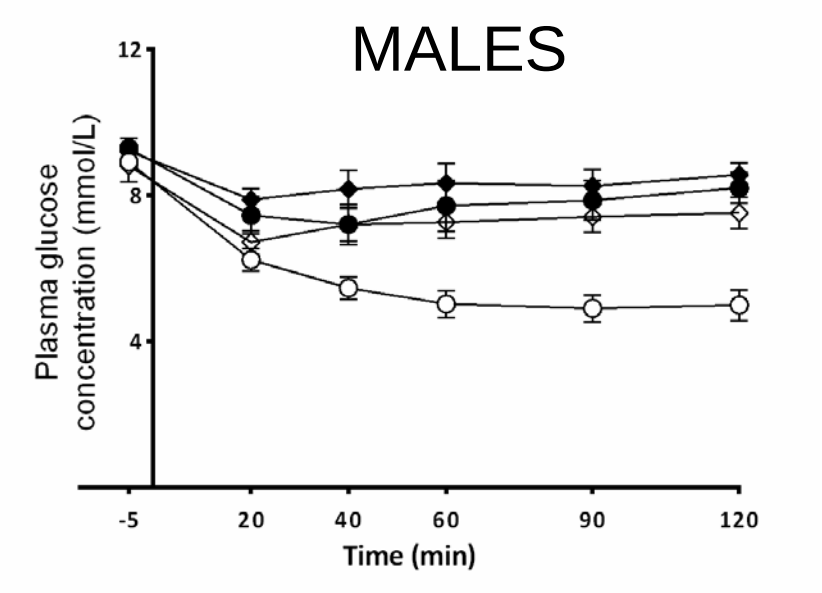


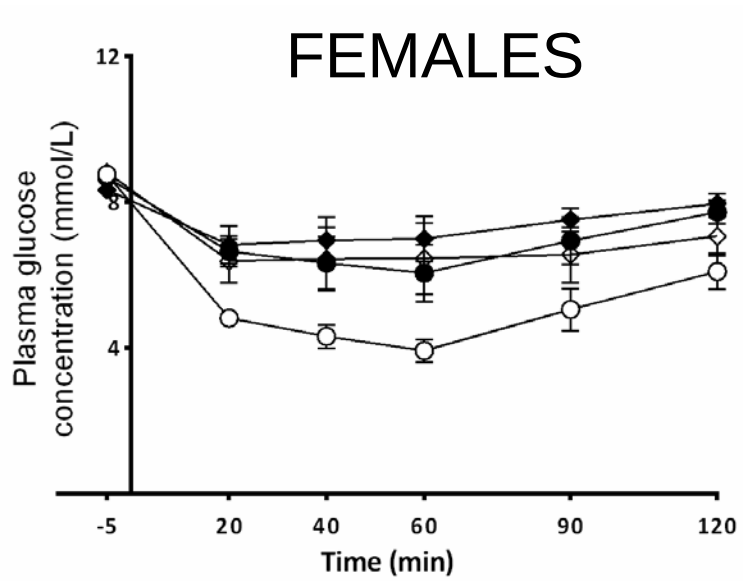




Gardebjer et al, FASEB J. 2015 Jul;29(7):2690-701

PCE causes insulin resistance in males AND females at 8 months

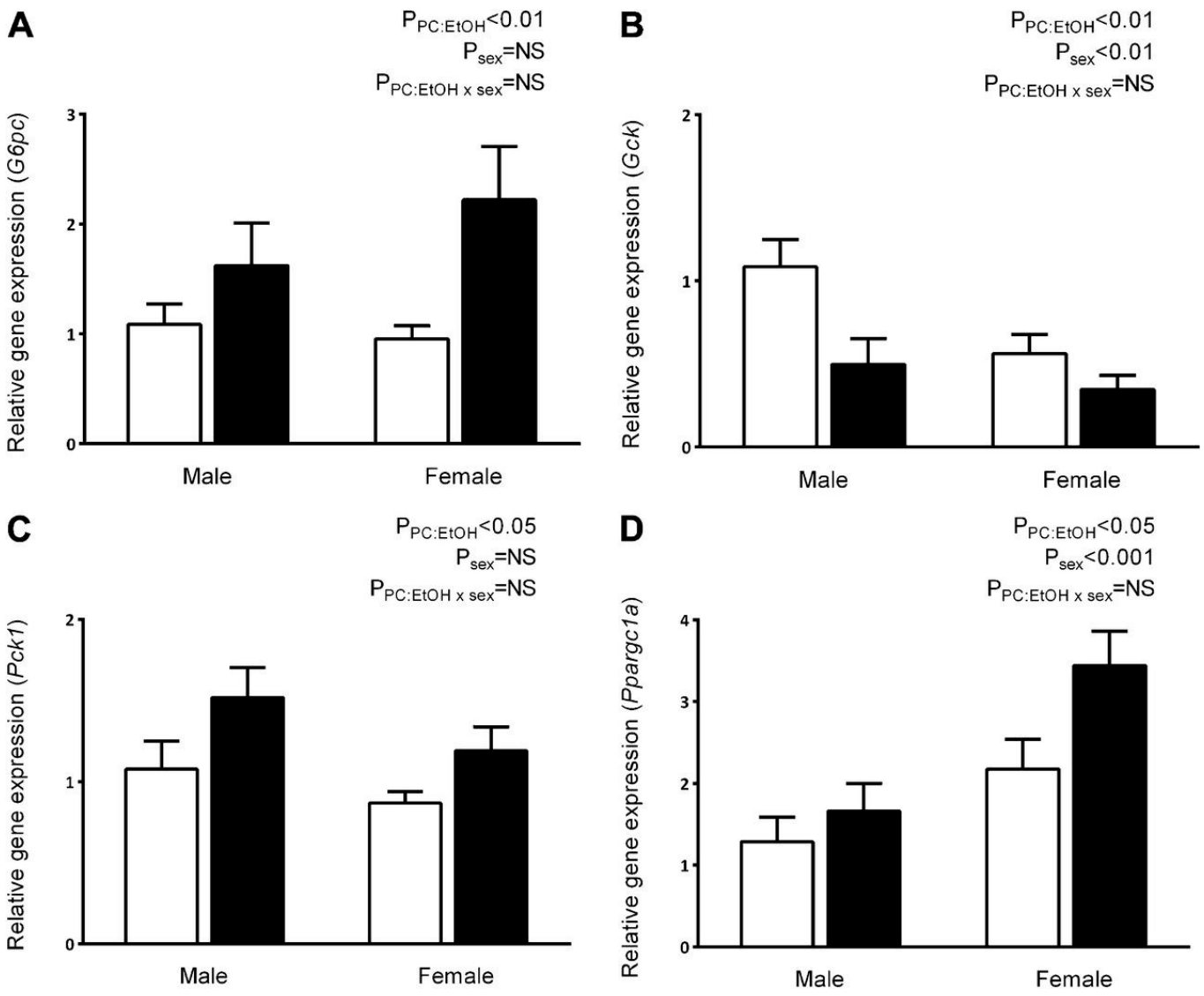




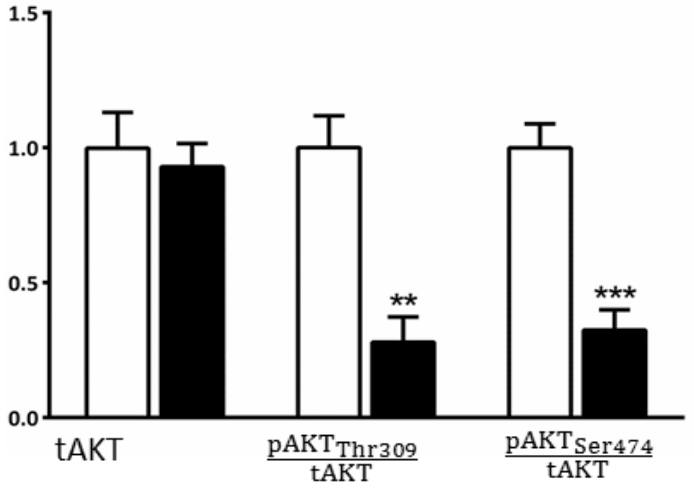
Increased fasting glucose (males)
Impaired response to GTT
Insulin resistance (both sexes)

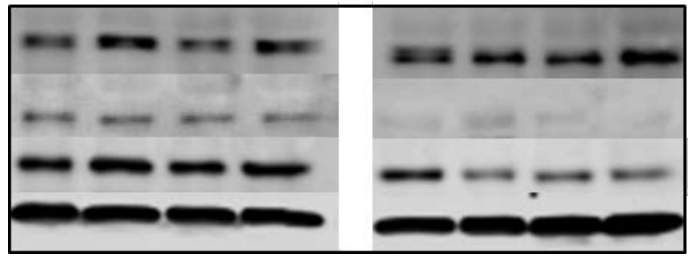
Gardebjer et al, FASEB J. 2015 Jul;29(7):2690-701

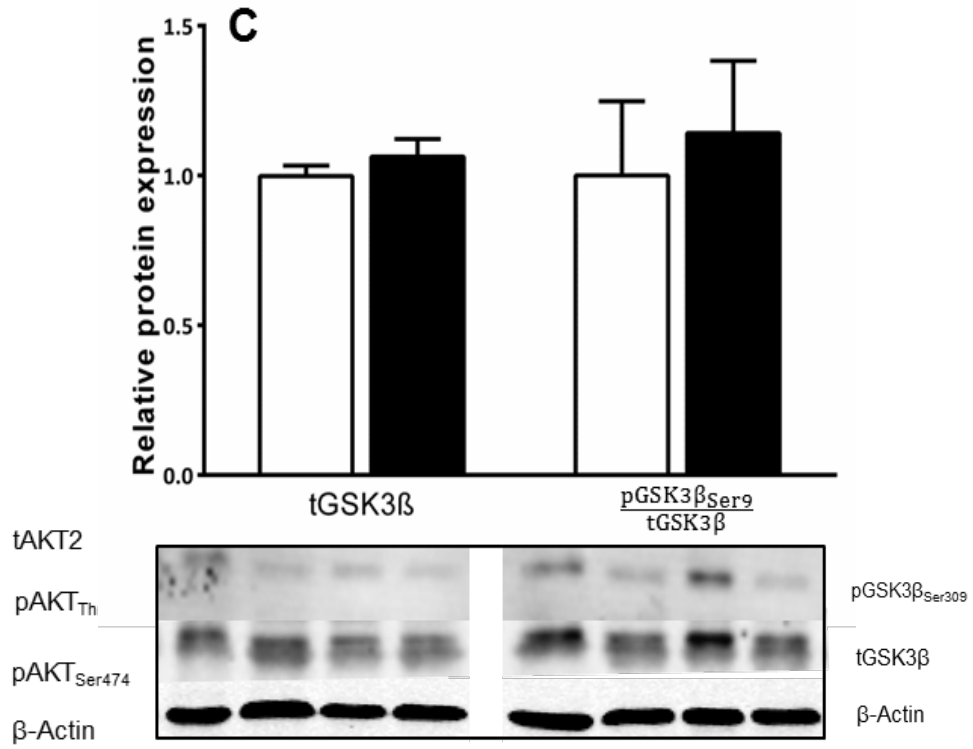
PCE: changes to hepatic gene expression



Altered insulin signaling in adipose tissue

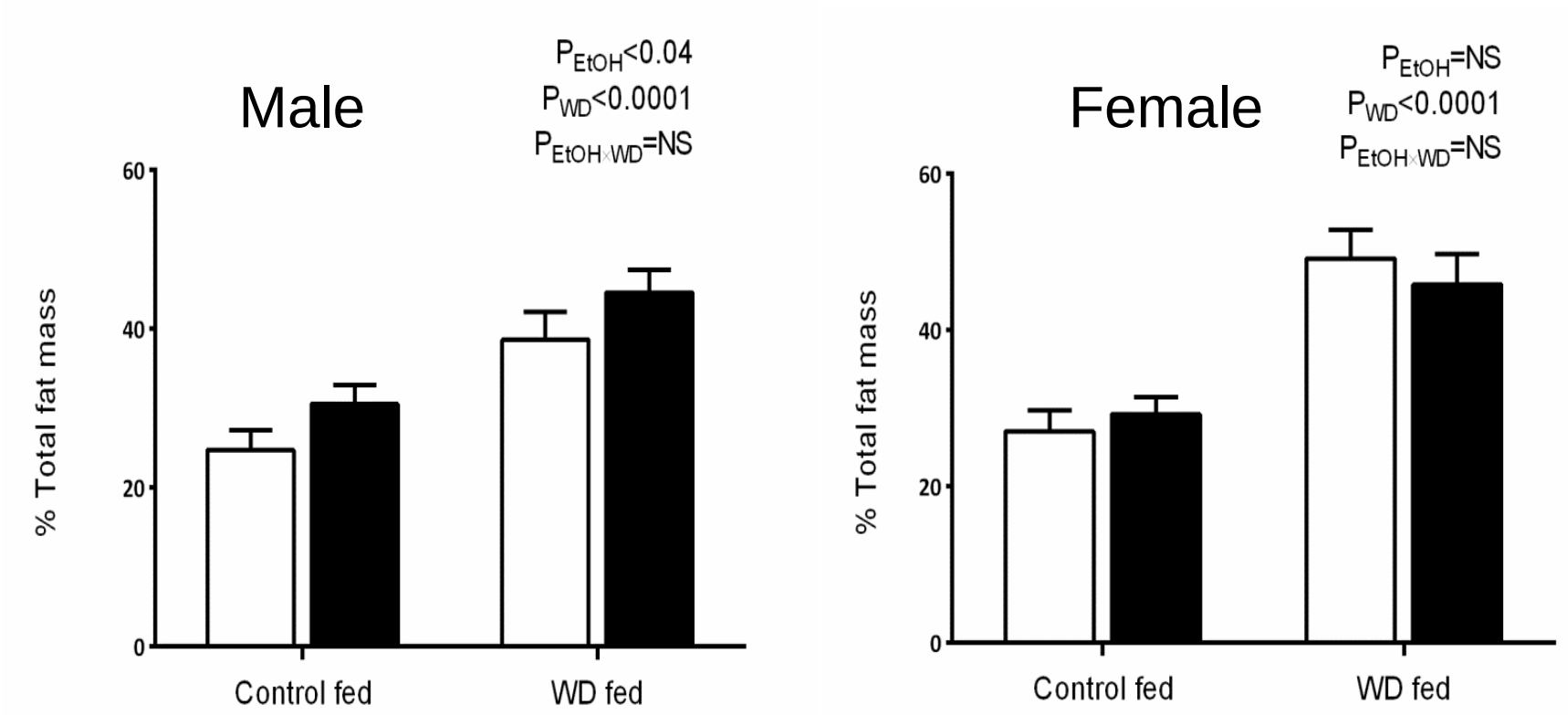






PCE: Altered hepatic gene expression and altered muscle and adipose (peripheral) insulin signaling

Programming of obesity



No differences in body weight
Abdominal fat – 'fat- thin Indian'

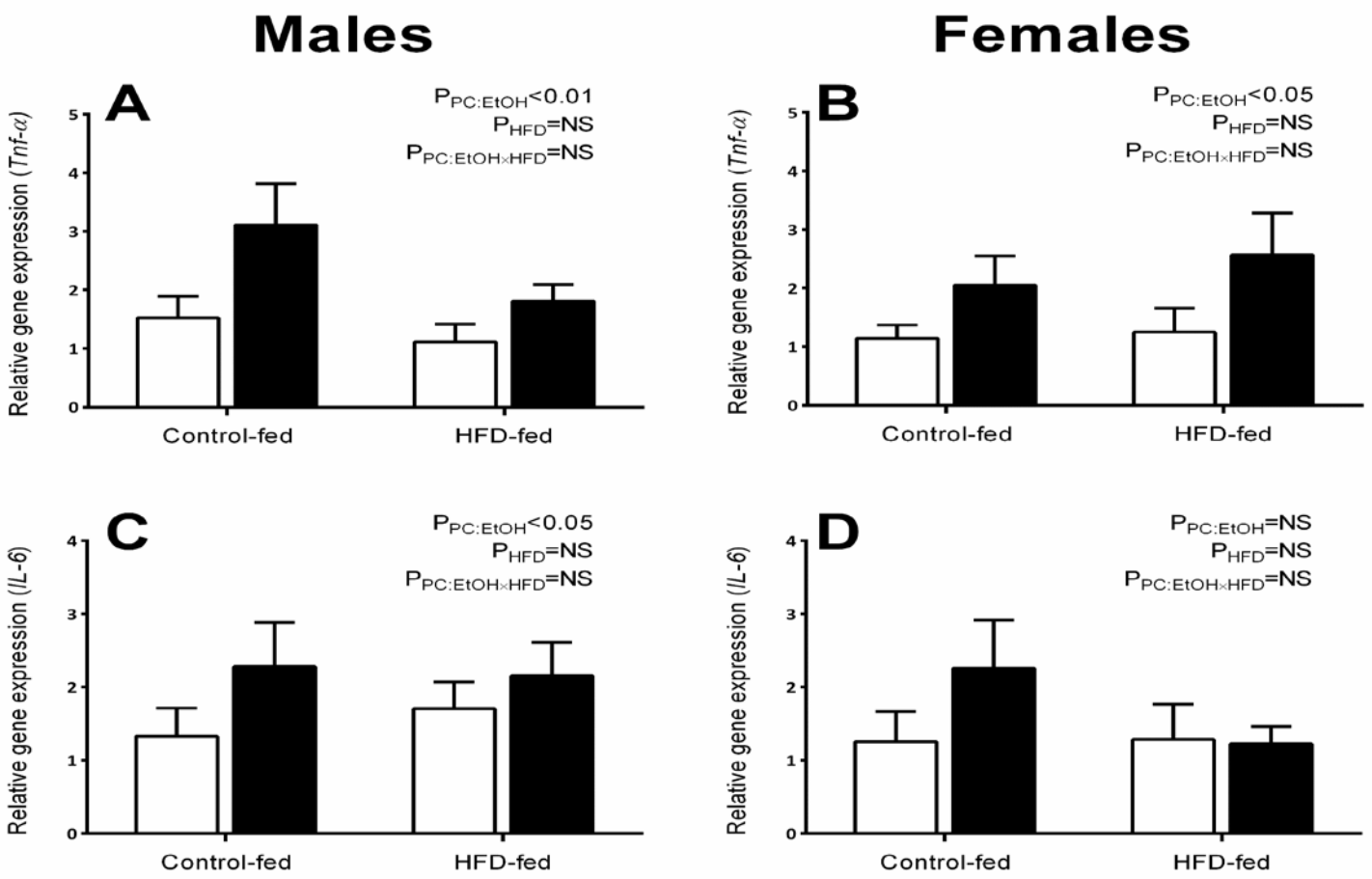
Gardebjer et al, Am J Physiol, 2018

Plasma hormones

*

8 months of age **Day 30**

PCE and inflammation



Increased fat deposition (in males) – abdominal fat
Increased expression of inflammatory genes,
Increased early life leptin.

Programming of metabolic disease: a role for altered circadian clock?

A role for circadian clock in metabolic disease

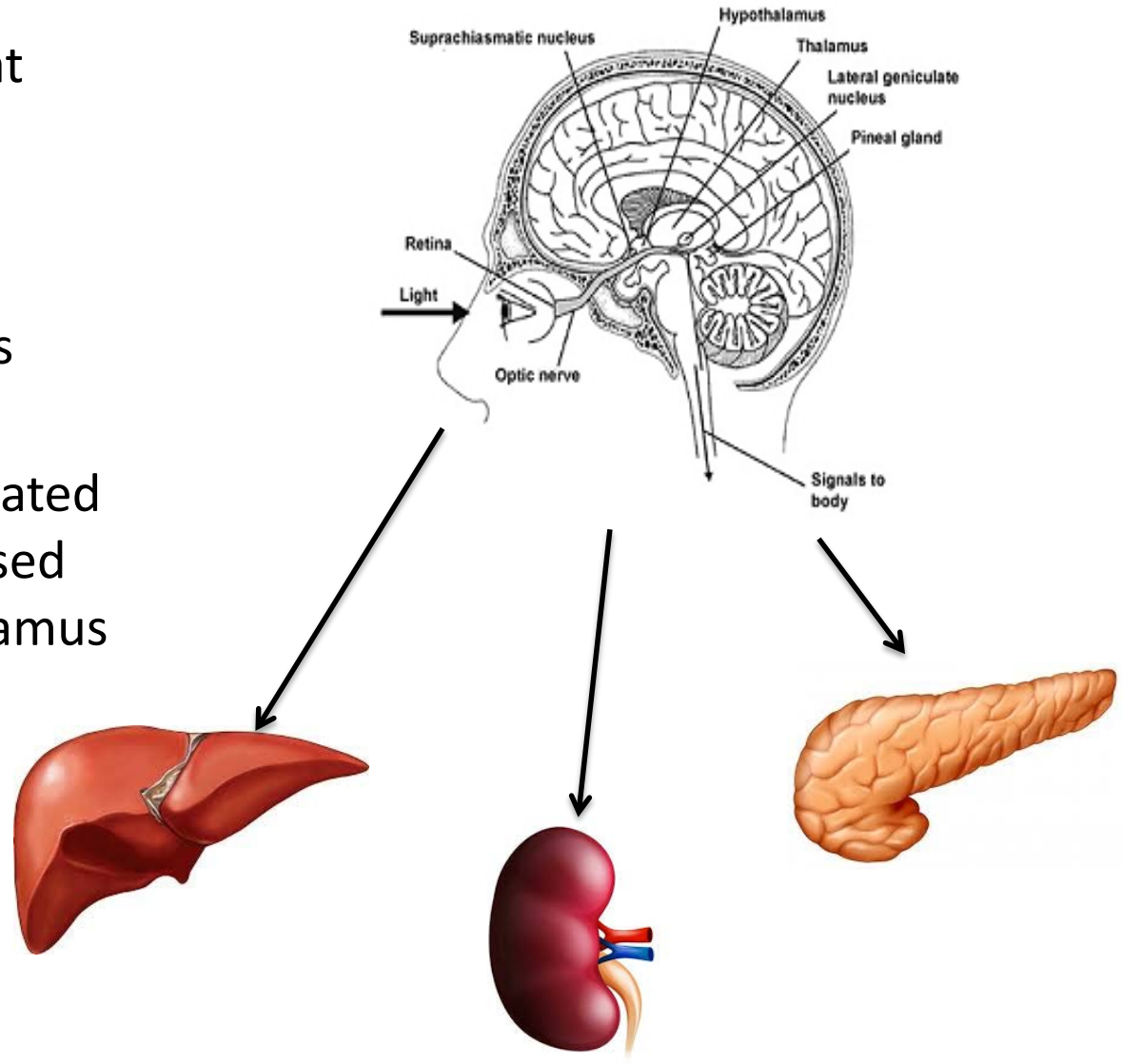
Ippei Shimizu[1,2], Yohko Yoshida[1,2] and Tohru Minamino[1]

Many human behaviors and physiological activities show circadian rhythms. Circadian rhythms generated by central and peripheral clocks maintain homeostasis, including the regulation of metabolic processes. Biological rhythmicity is important for metabolic health, but circadian rhythms are affected and impaired by nocturnal activities and irregular food intake in modern society. Disruption of sleep is an established risk factor for diabetes and is known to promote systemic metabolic dysfunction in both humans and rodents. Metabolic stress promotes circadian clock disorders and modulation of clock gene expression has a causal role in the development of metabolic dysfunction. Maintenance of a physiological circadian rhythm is crucial for metabolic health and is an important strategy for combating obesity.

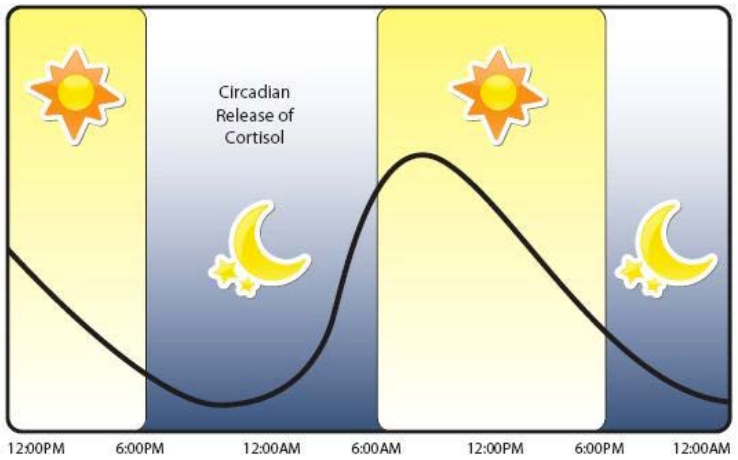
Hypertension Research advance online publication, 18 February 2016; doi:10.1038/hr.2016.12

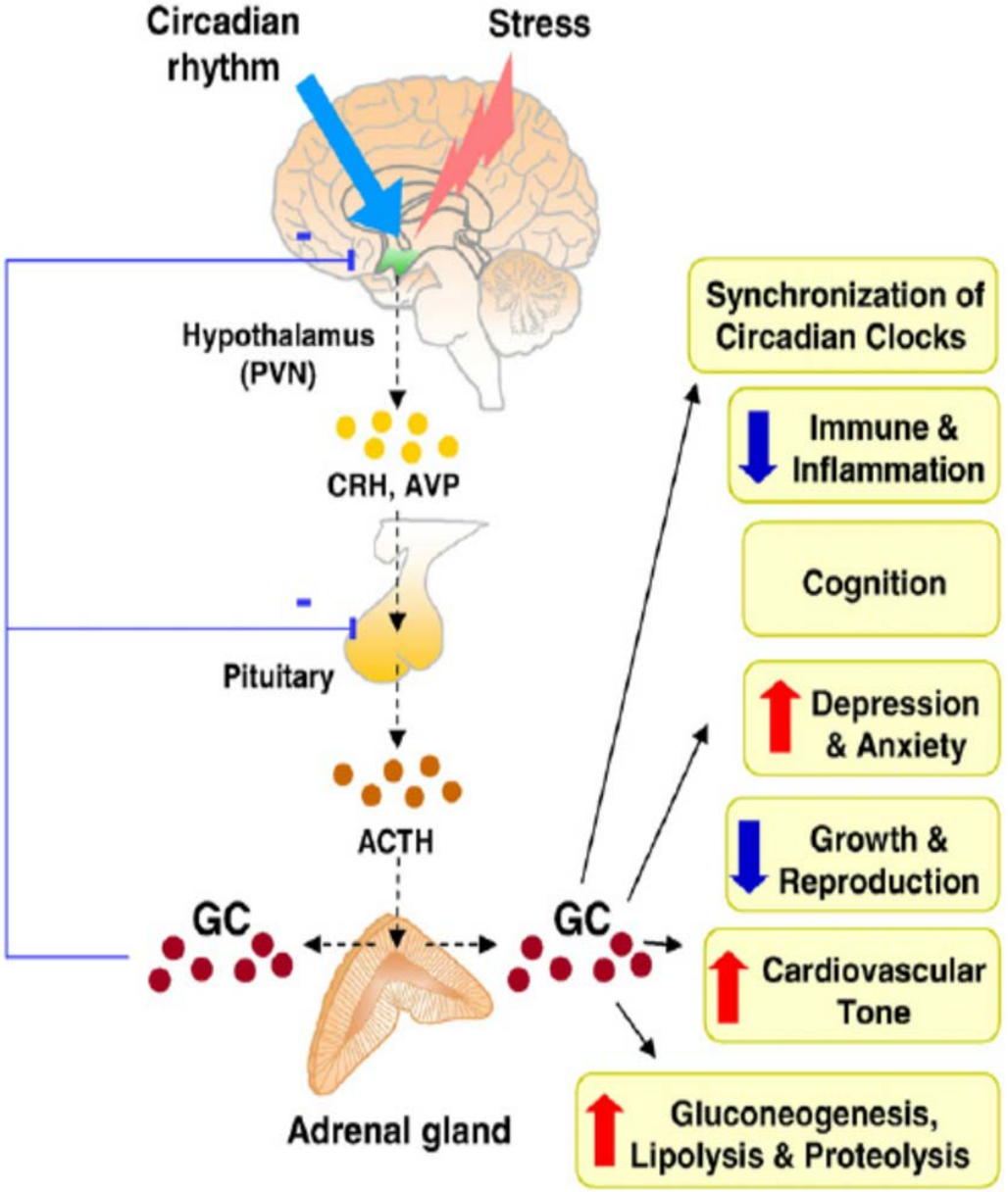
Circadian Rhythm

- Biological processes that oscillate over 24hr day
  - hormone secretion, sleep/wake cycles, glucose homeostasis immune function
- Peripheral ‘clocks’ regulated by a ‘master clock’ housed within SCN of hypothalamus

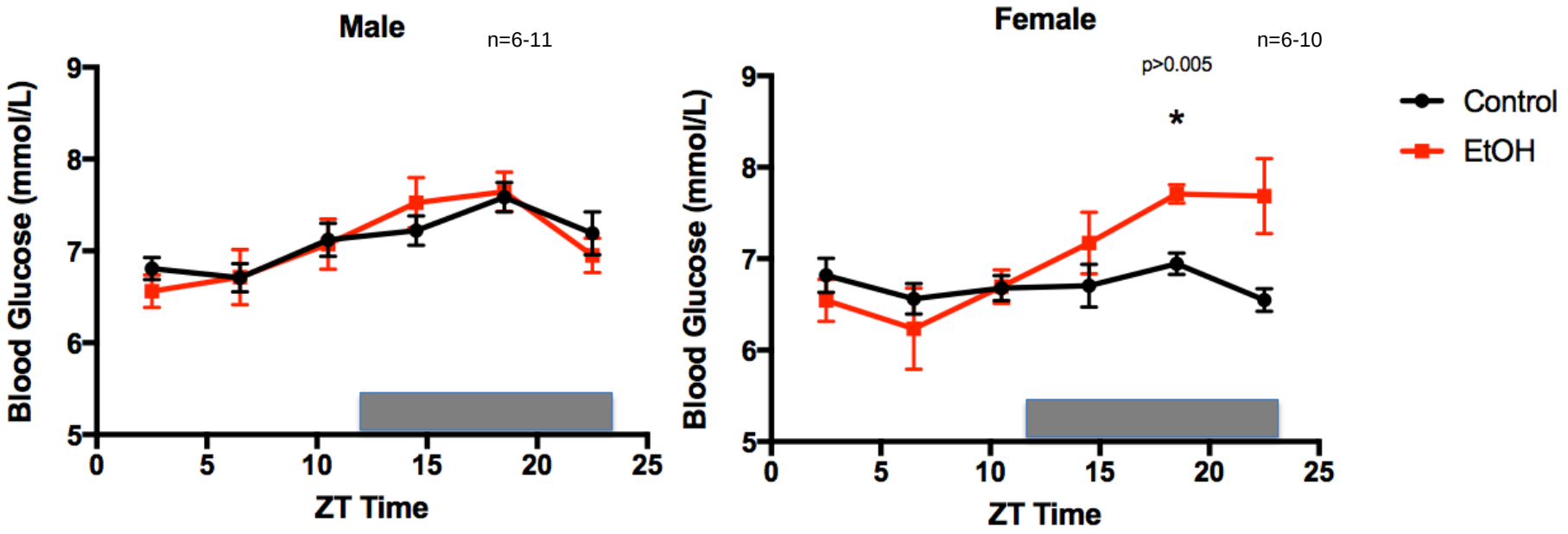


Circadian regulation of gluconeogenesis and cortisol secretion



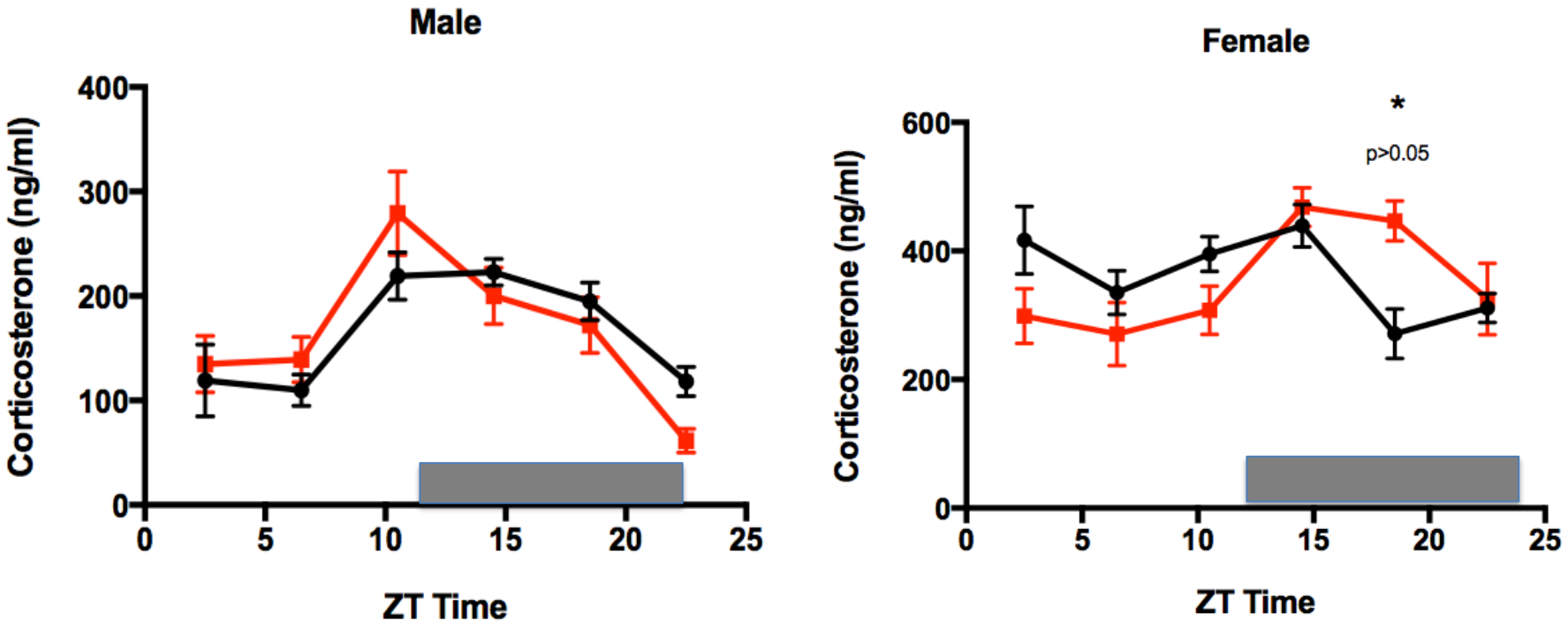


Programming of circadian rhythms



No differences in eating behaviour

Programming of circadian rhythms



ELSEVIER

Alcohol

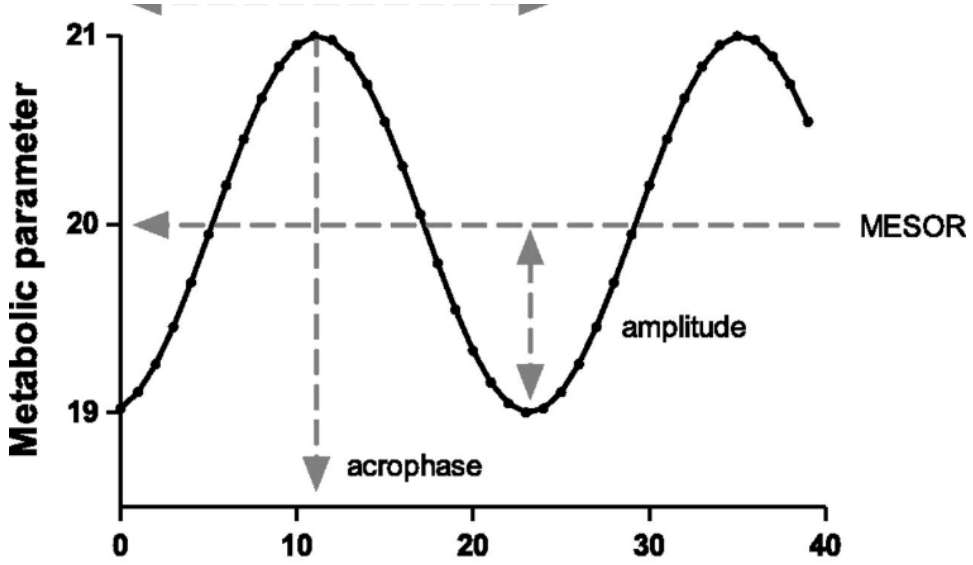
journal homepage: http://www.alcoholjournal.org/

Salivary cortisol levels are elevated in the afternoon and at bedtime in children with prenatal alcohol exposure

Kathy Keiver [a,*], Chris P. Bertram [a], Alison Pritchard Orr [a], Sterling Clarren [b]

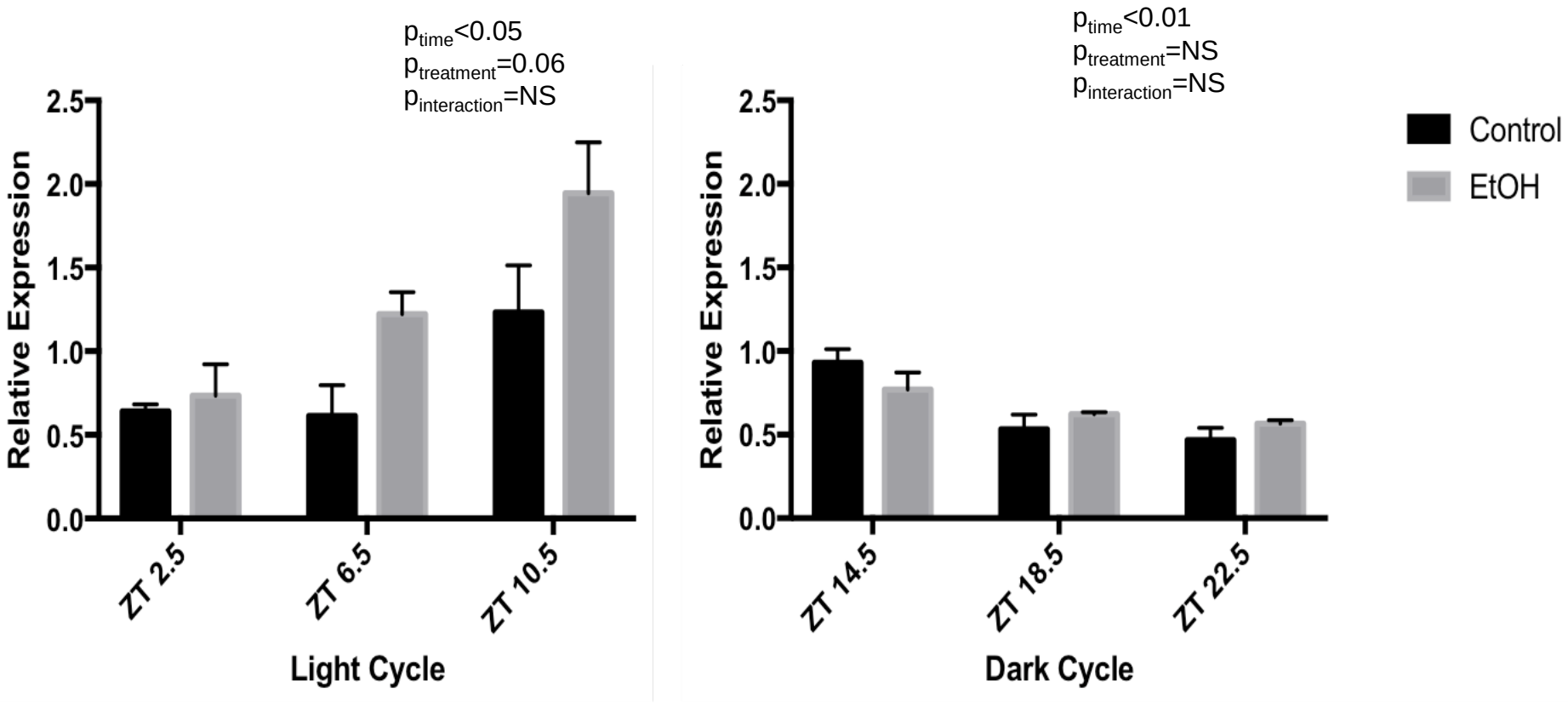
[a] Department of Kinesiology and Physical Education, University of the Fraser Valley, 33844 King Road, Abbotsford, British Columbia V2S 7M8, Canada
[b] Centre for Community Child Health Research, Canada Northwest FASD Research Network, Vancouver, British Columbia, Canada

PCE alters circadian rhythms



Corticosterone	Female Control	Female Ethanol	p
Mesor Amplitude Acrophase	354.2 ± 16.3 36.9 ± 23.5 9.47 ± 2.37	352.6 ± 16.8 102.2 ± 24.1 16.81 ± 0.87	ns p=0.05 p<0.005
	Male Control	Male Ethanol	p
Mesor Amplitude Acrophase	163.90 ± 8.36 66.80 ± 11.90 14.212 ± 0.664	159.3 ± 11.50 90.7 ± 16.6 12.183 ± 0.699	ns ns p<0.05

G6pc Gene Expression - Females



Potential Mechanism

PCEtOH

Epigenetic change → Altered CNS 'clock'

Altered Circadian Rhythm

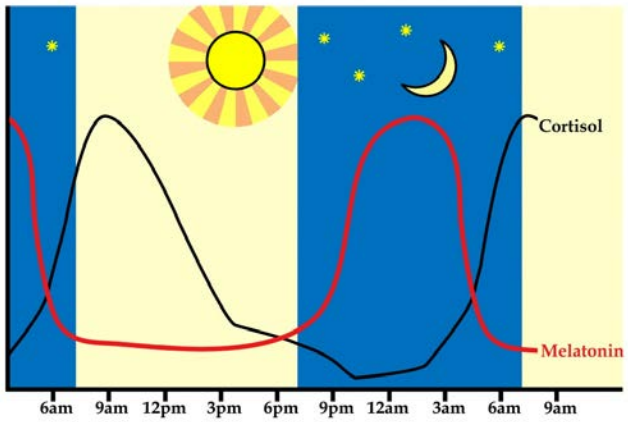
↑ Corticosterone secretion

↑ Blood glucose

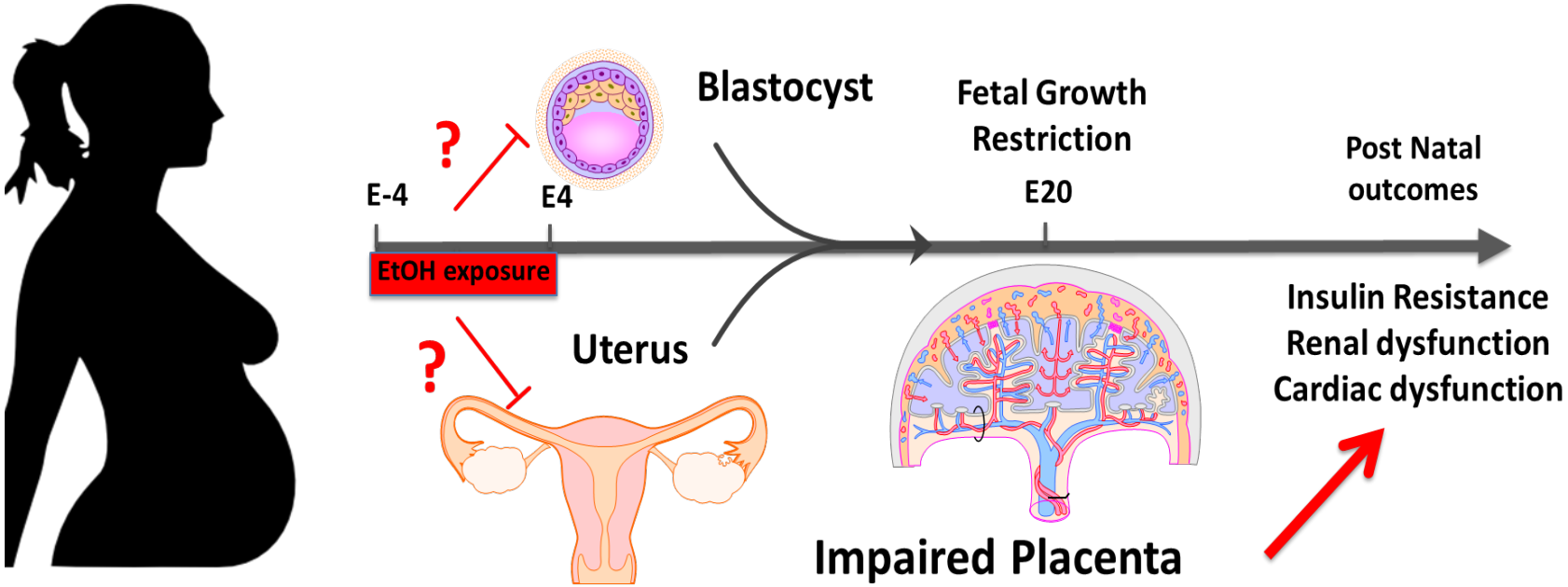
Altered HPA axis regulation

Corticosterone secretion shifted forward

Metabolic Disease

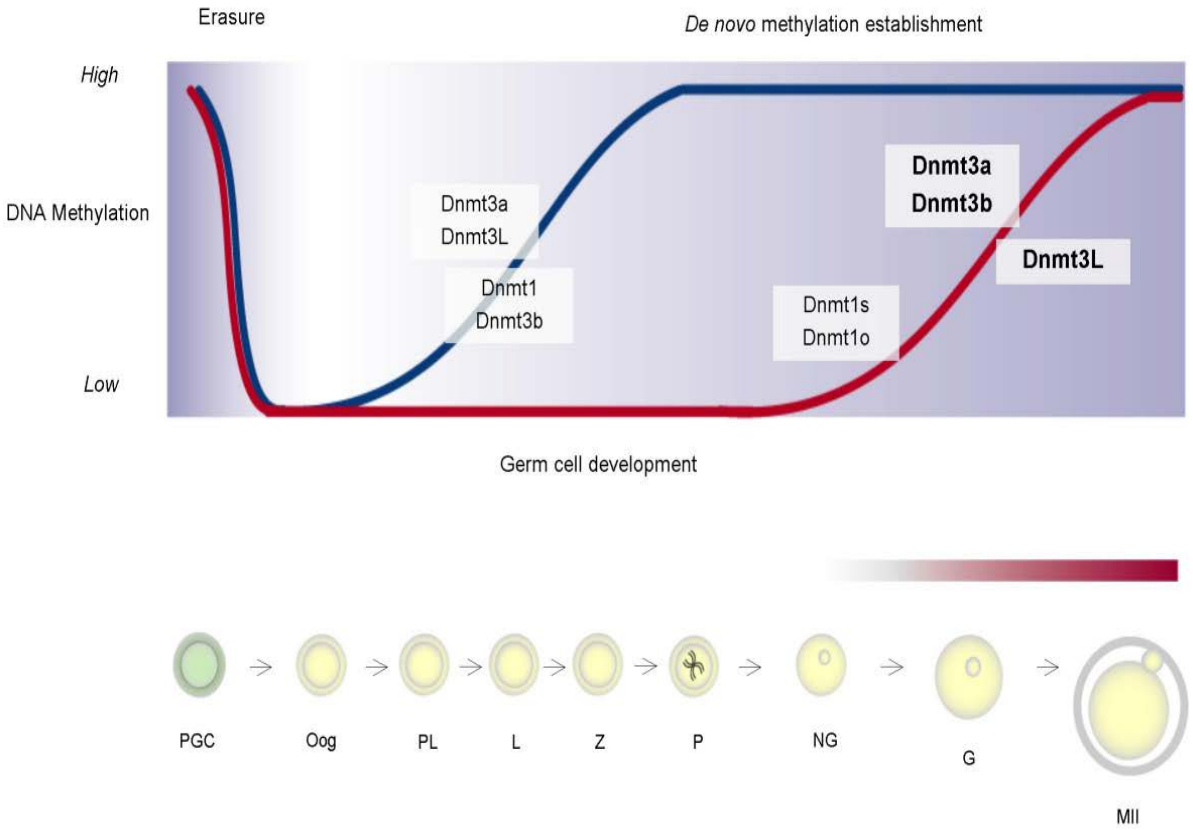


How are these effects mediated?



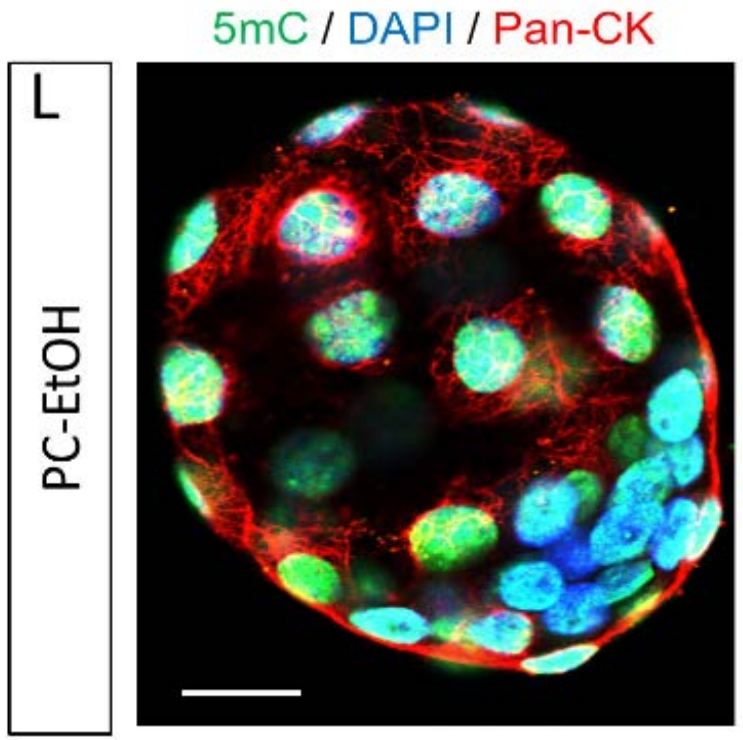
- Epigenetic effects?
- Effects on the blastocyst
- Effects on the uterus?
- Effects on the placenta?

The periconceptional period is susceptible to epigenetic modification



DNA methylation
Histone modifications
miRNAs

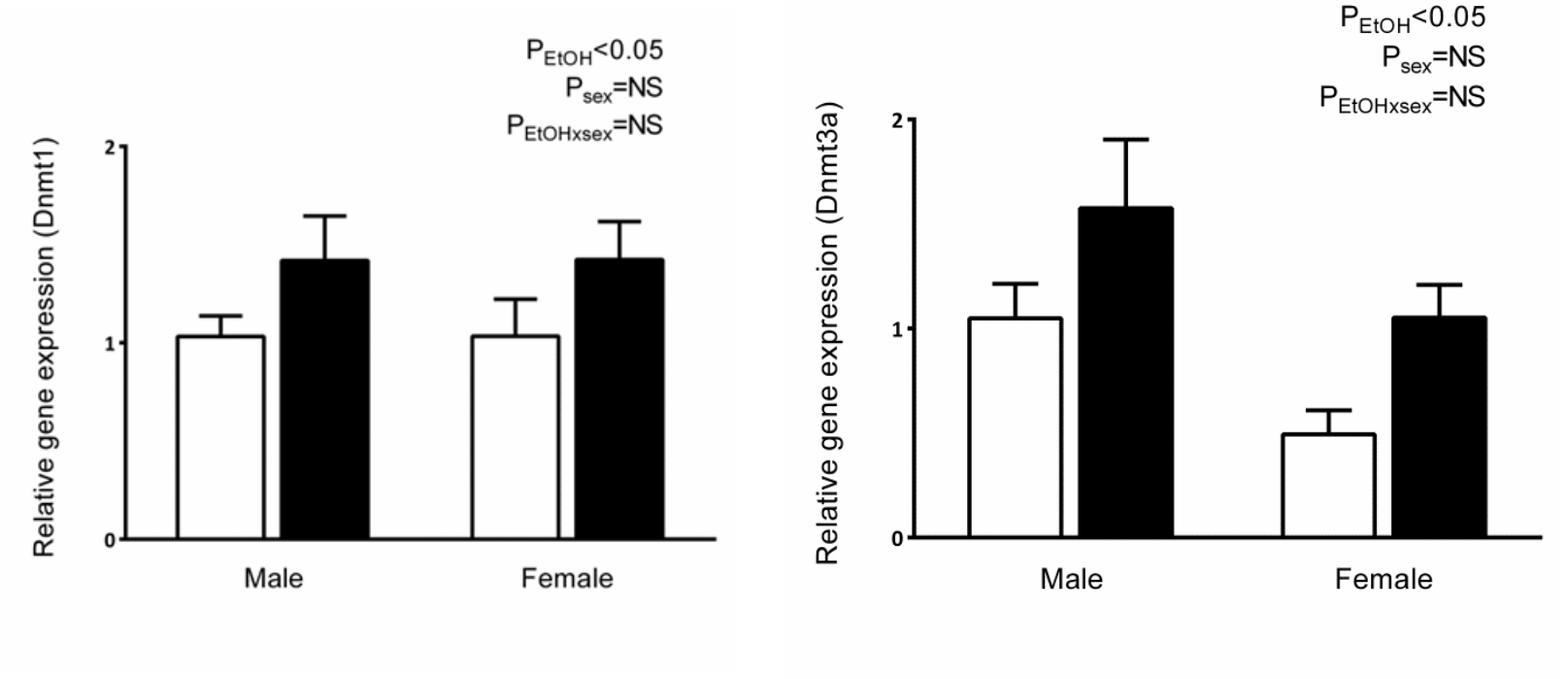
Alter DNA methylation?



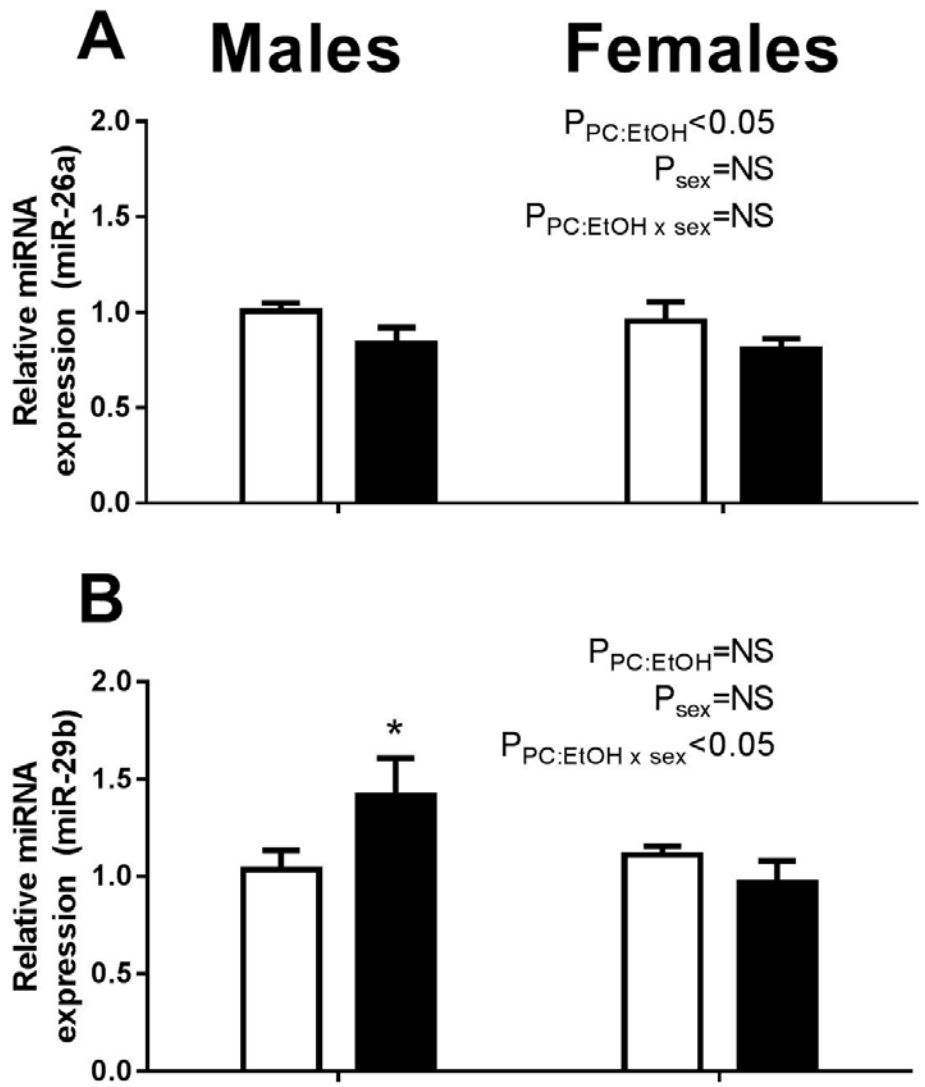
Nuclear 5MC labelling (green) was increased in flushed day 5 blastocysts exposed to PCE. Blue labelling (DAPI) indicates cell nuclei whilst red labelling (pan-cytokeratin) labels cell membranes.

PCE results in changes in DNMT's

Fetal Liver – E20



Gardebjer et al, FASEB J, 2015



PCE alters miRNA's regulating leptin and inflammatory genes (adult)

Gardebjer et al, Am J Physiol, 2018

Prenatal alcohol exposure may ‘program’ metabolic syndrome/disease?

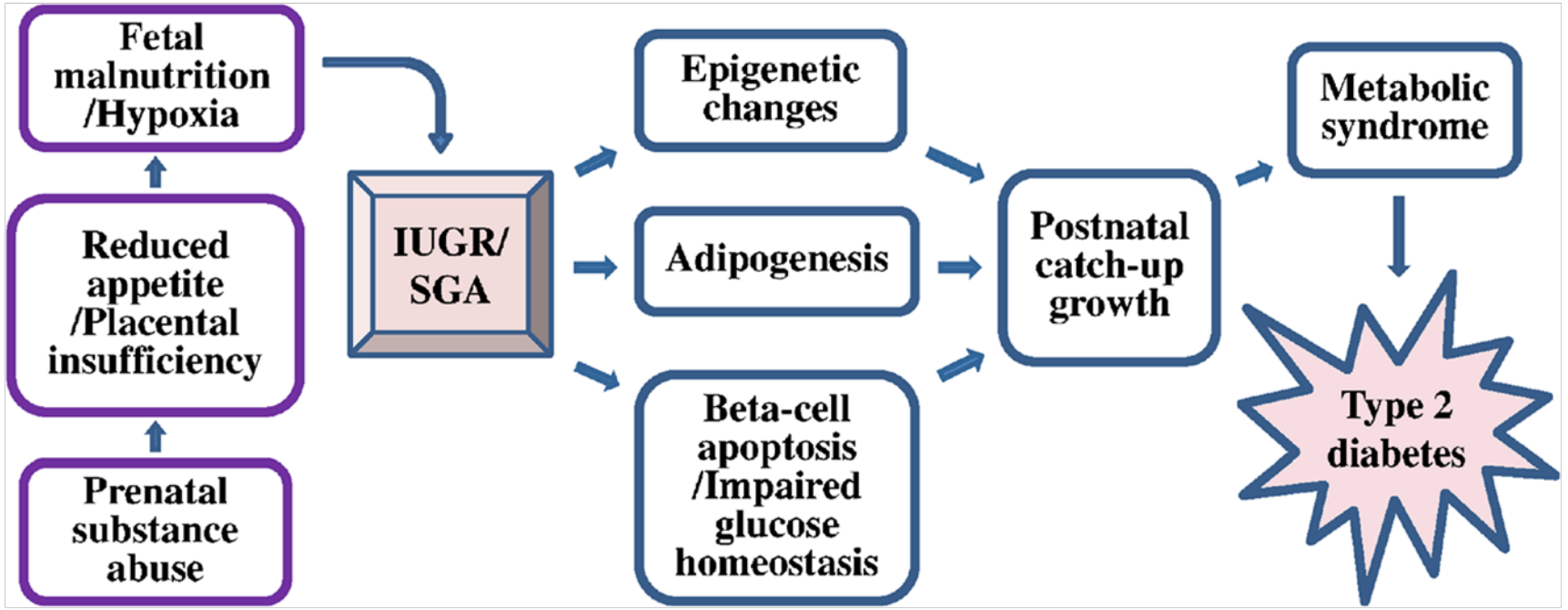


Fig. 1 A hypothetical scheme of the main mechanisms linking prenatal exposure to substance of abuse to development of metabolic syndrome and T2D in adult life

Curr Diab Rep (2015) 15: 48

Take home messages and questions going forward:

- Exposure to alcohol in rat models can later glucose homeostasis and cause insulin resistance, a risk for increased fat deposition and changes in circadian rhythms.

Does this also occur in adults with FASD?
Checking of fasting glucose at an early age?
Guidance on interaction with lifestyle factors