Biological Determinants: Developmental Origins

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Biological Determinants: Developmental Origins

1. Overview of developmental programming and evidence for the importance of the developmental environment in determining offspring – particularly female offspring phenotype.

2. Mechanisms whereby a female offspring's phenotype is changed by her developmental environment thus putting her own later pregnancy at risk.

3. Transgenerational effects.

4. Action.

Programming

The process through which a *stimulus* or *insult* establishes a *persistent* response.

Developmental programming hypothesis

Exposure during a *critical period* in development may influence phenotype - life time function and health.

Developmental Programming

The idea that our life-time health is as much impacted by the conditions under which we develop in the womb and early life as by our genes is a paradigm shift in our thinking of what needs to be done to improve the health of the nation. We need to think in terms of gene-environment interactions.

We pass more biological milestones before we are born and in the early months as a baby than at any other time in our lives.

How we pass these milestones will be greatly affected by our very first environments, the womb and immediately after birth.

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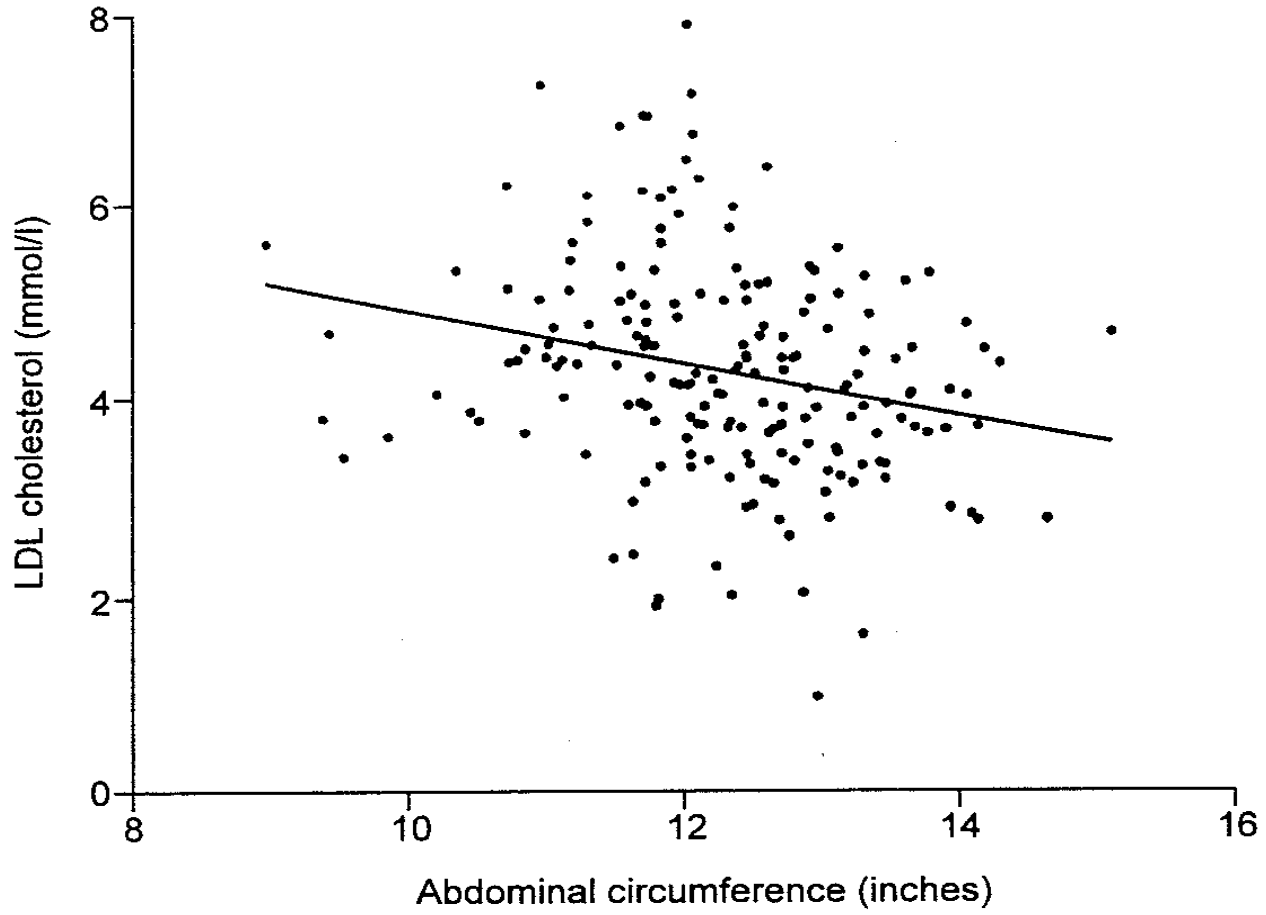
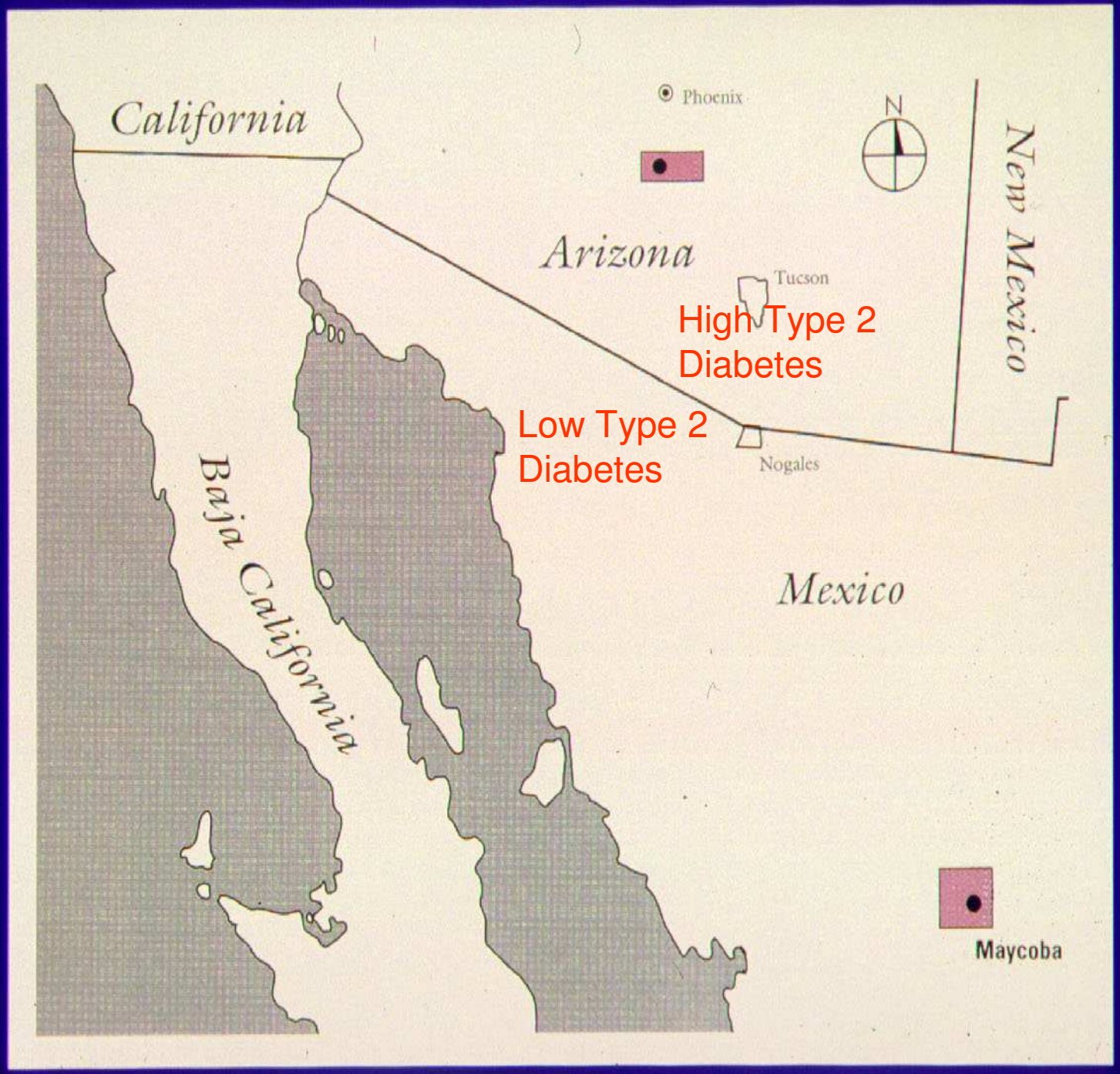


Fig. 5.1 Low density lipoprotein cholesterol concentrations plotted against abdominal circumference at birth, adjusted for duration of gestation, in men and women aged 50–53 years.

Blood cholesterol in men and women at the age of 50 can be related to the extent to which they had to protect their brain when they were fetuses

How do we know that nutrition in pregnancy is important?

A young Pima woman


California
Phoenix
N
New Mexico
Arizona
Tucson
High Type 2
Diabetes
Low Type 2
Diabetes
Nogales
Baja California
Mexico
Maycoba

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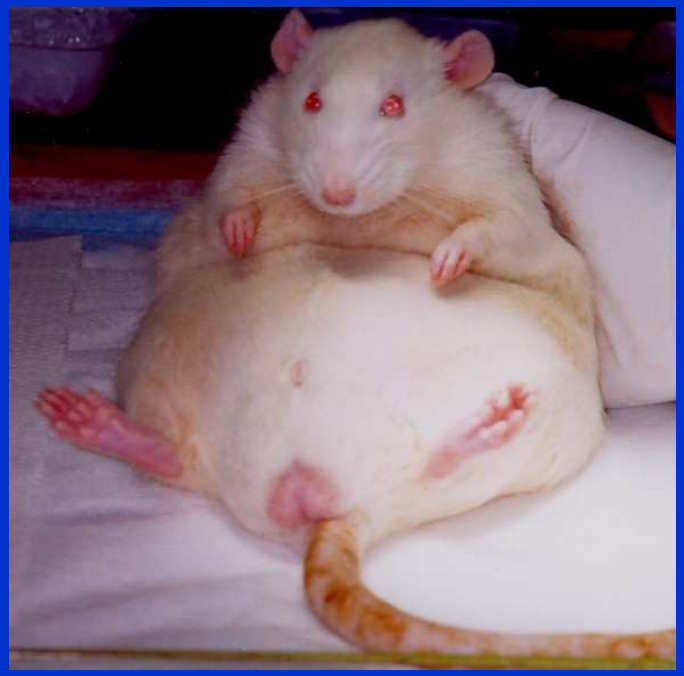
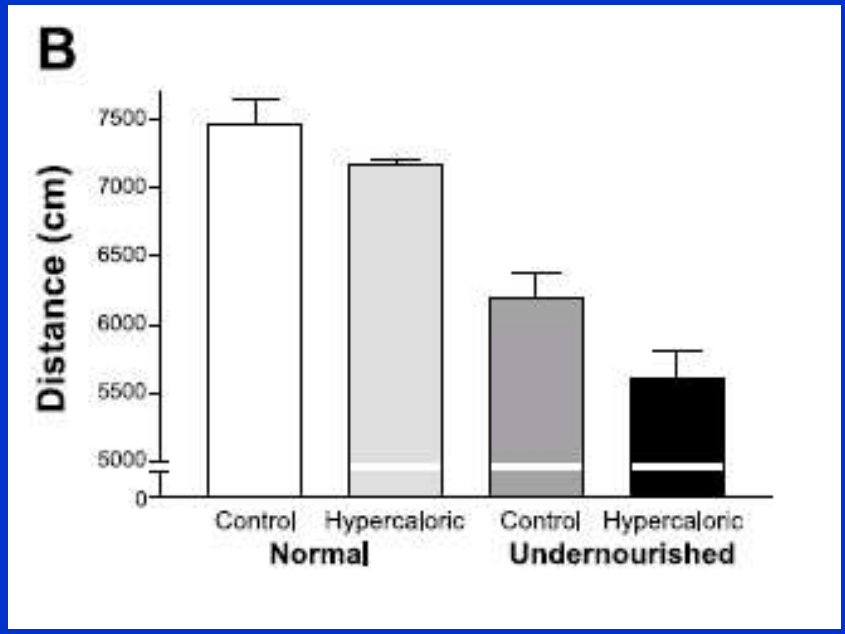
The couch potato rat.

Severe maternal undernutrition (30% normal diet) induces increased fat mass and reduces offspring locomotor activity.

Vickers MH et al., 2000;2001; 2003

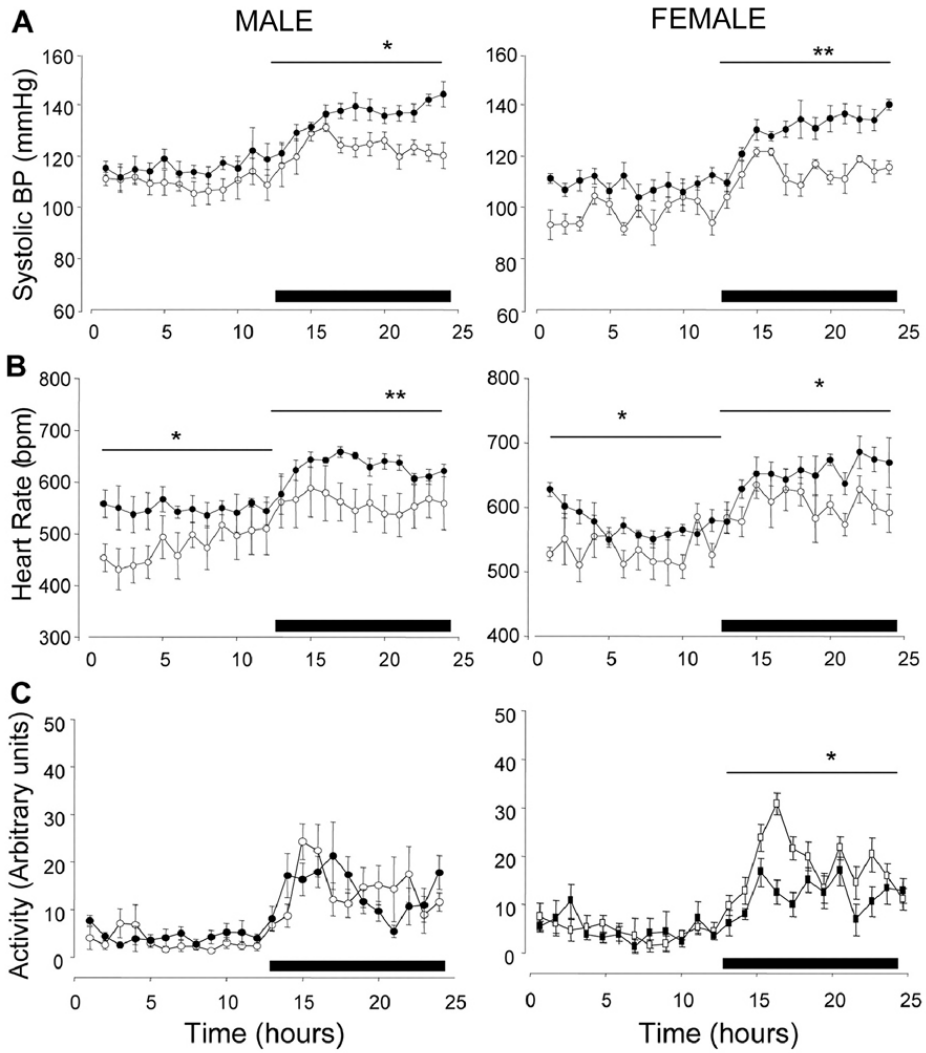
Voluntary locomotor activity

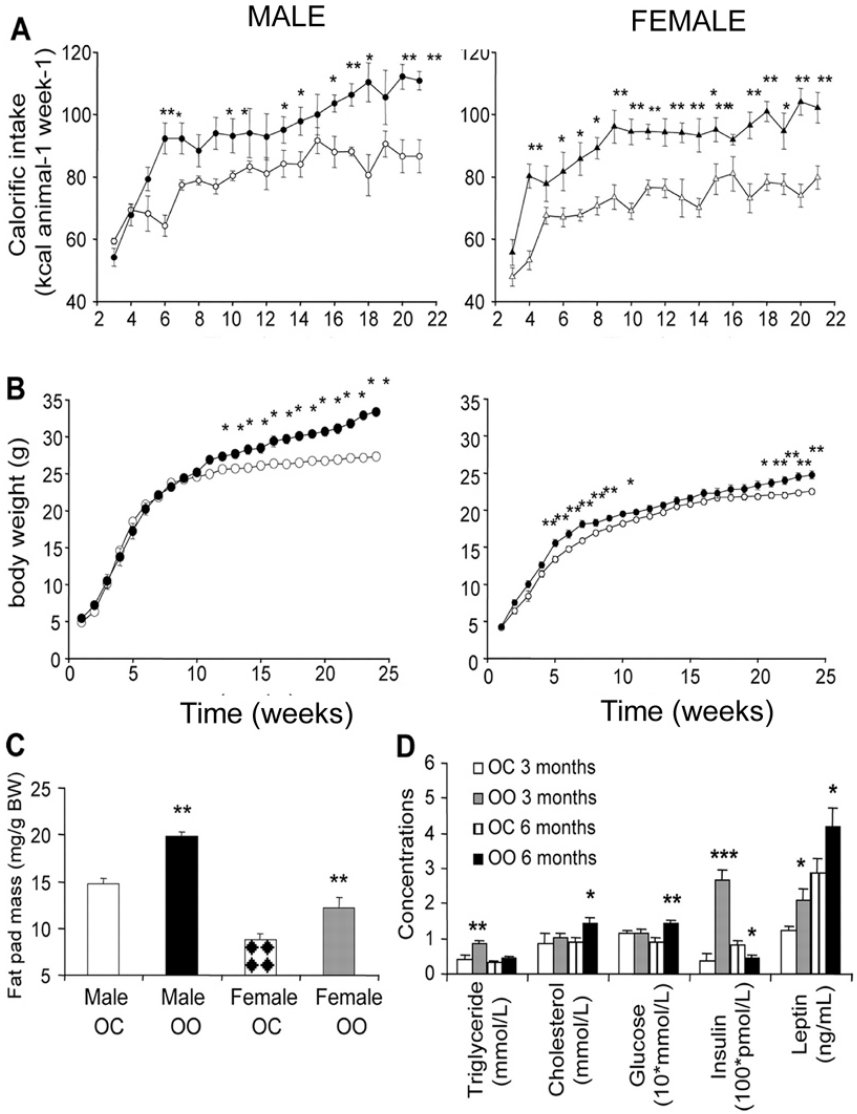


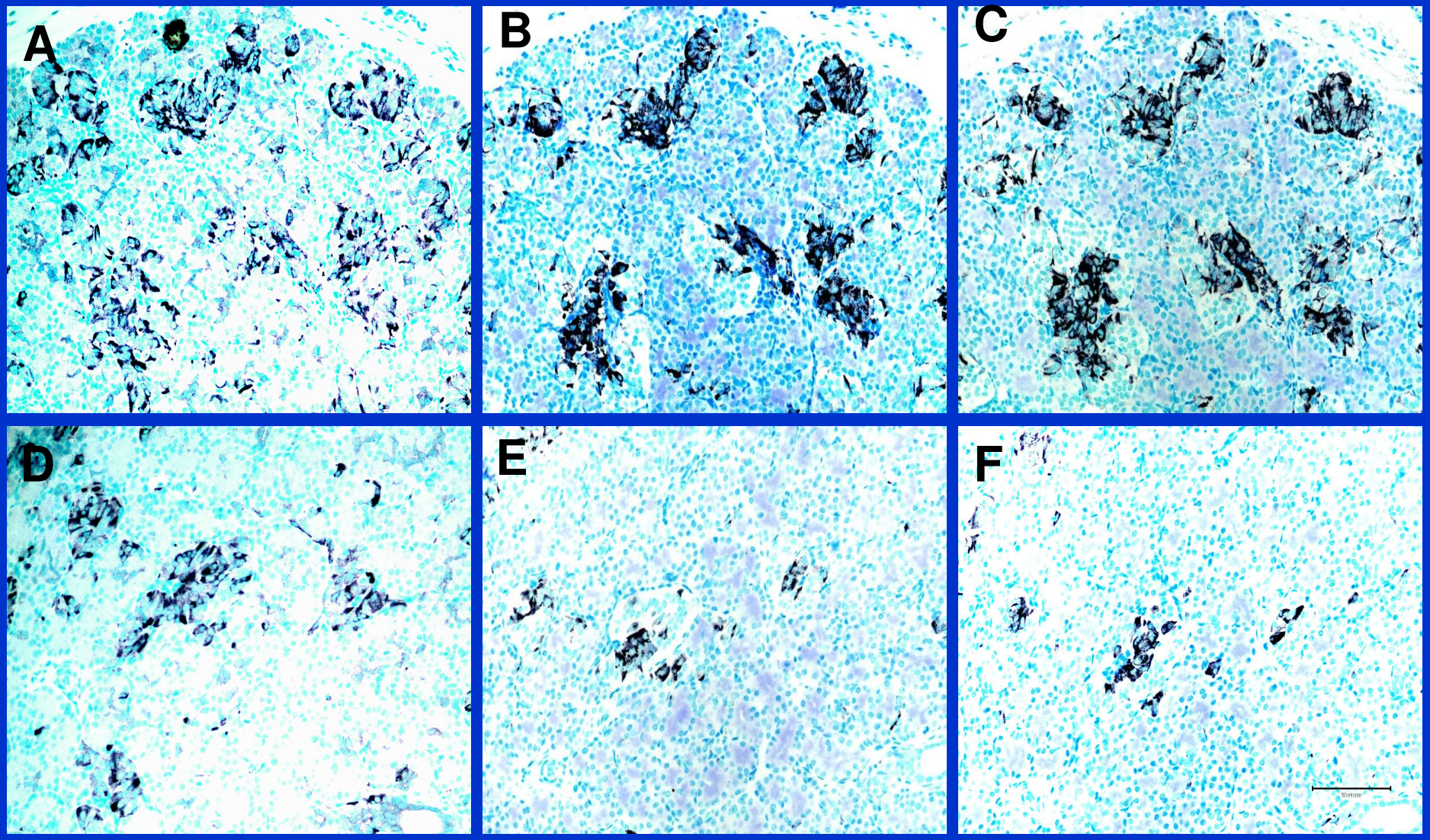


Cardiovascular variables allometry and plasma analytes in six month old offspring of fat mice.

Samuelsson, A.-M. et al. Hypertension 2008;51:383-392

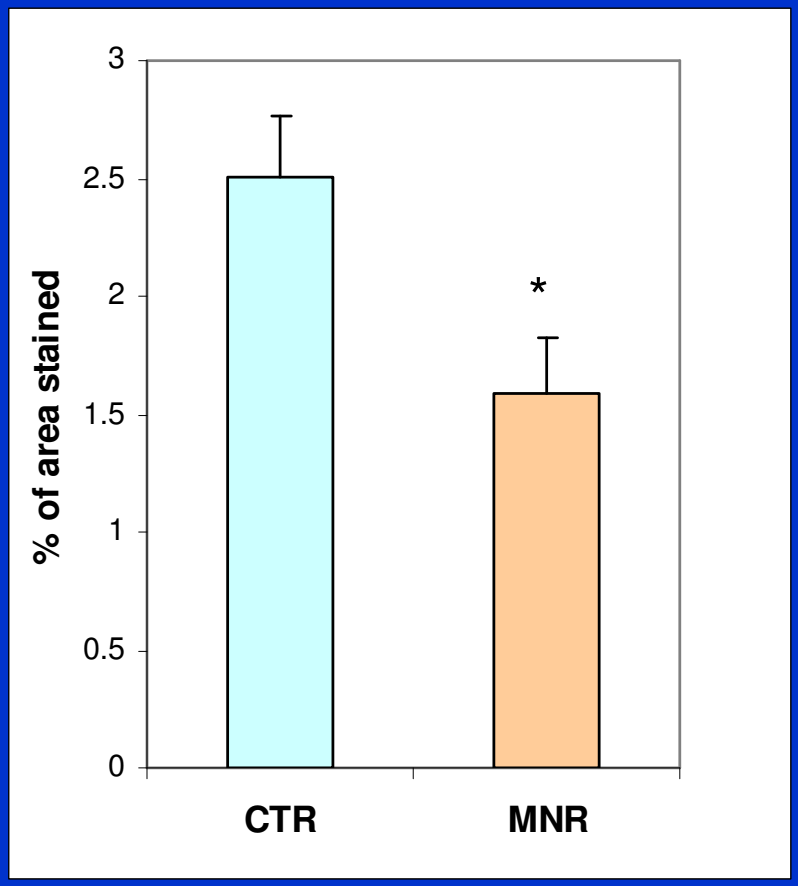


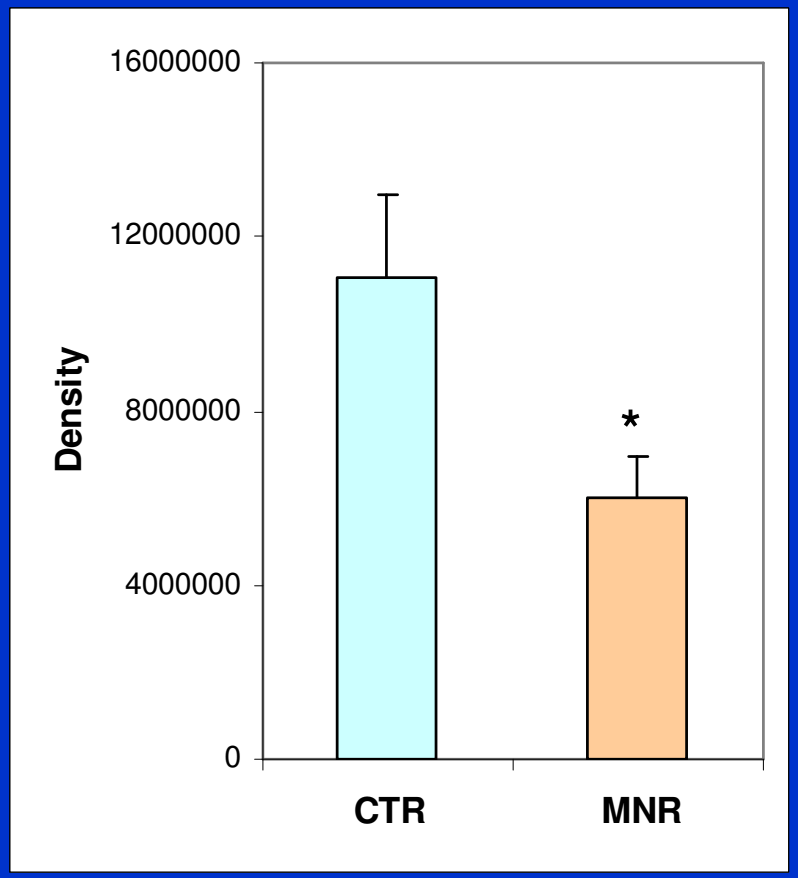




Immunohistochemistry in 0.9 G fetal baboon pancreas CTR (A-C) and MNR (D-F). IGF-1 (A,D); IGF-2 (B,E) and insulin (C,F).

Insulin Protein in 0.9G Baboon Fetal Pancreas





Fetal pancreatic Insulin fraction and density from *ad lib* fed controls baboons (CTR, n=7) or nutrient restricted (MNR; fed 70% CTR; n=7) from 0.16 to 0.9G. Data M ± SEM. **p< 0.05*.

Effects of maternal obesity on fetal development in the sheep.

The sheep is widely used as a biomedical model for human pregnancy, and is the ***only*** model large enough to study the challenged fetus directly combined with an evaluation of post-natal effects.

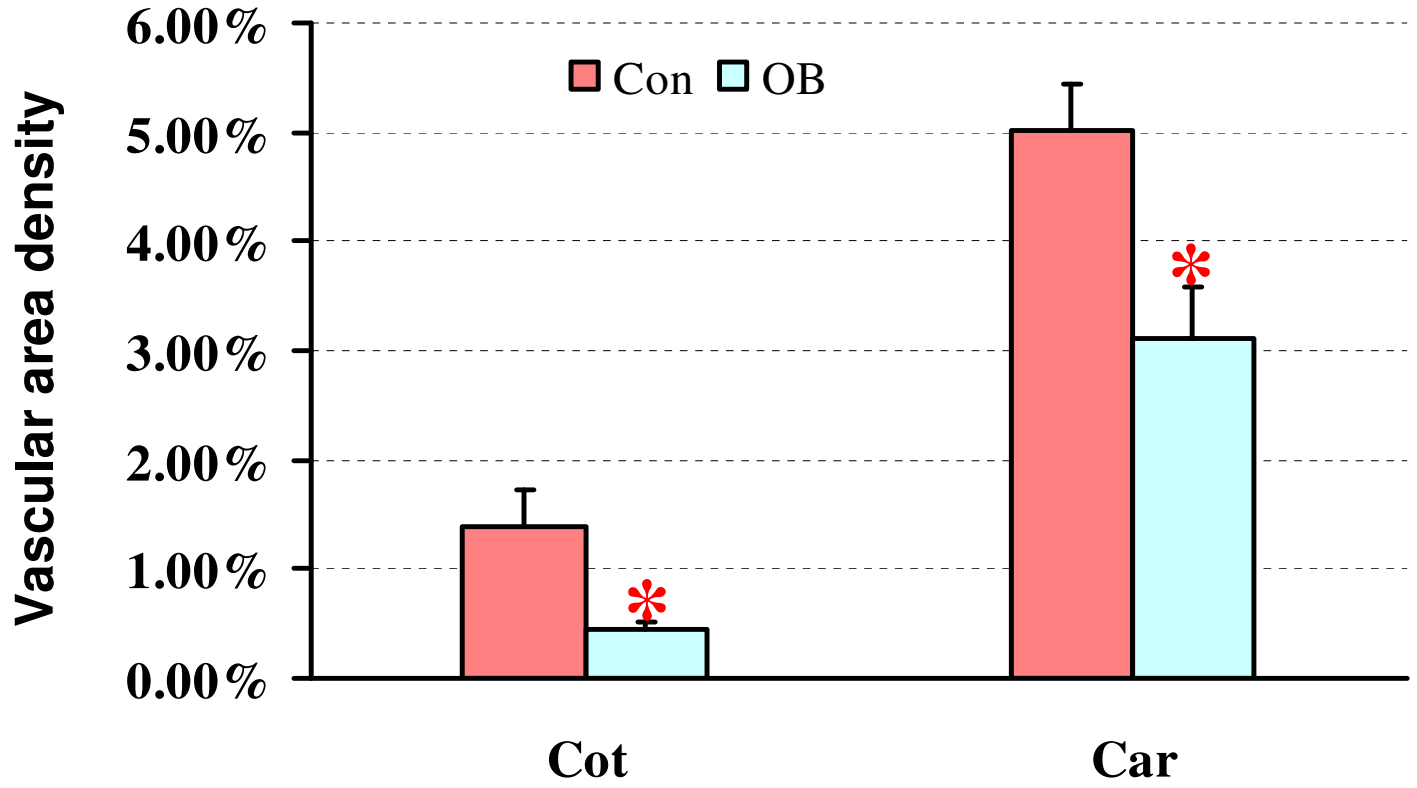
Methods

- Multiparous Western Whiteface ewes carrying singleton fetuses were fed a high energy diet at 100% (controls) or 150% (Obese) of NRC recommendations from 60 days before conception to day 75 of gestation.
- A subset of ewes were subjected to a GTT on day 75.
- A second set of ewes were necropsied on day 75 of gestation and the fetus recovered.
- A third set of ewes were allowed to deliver.

The first half of gestation is critical for:

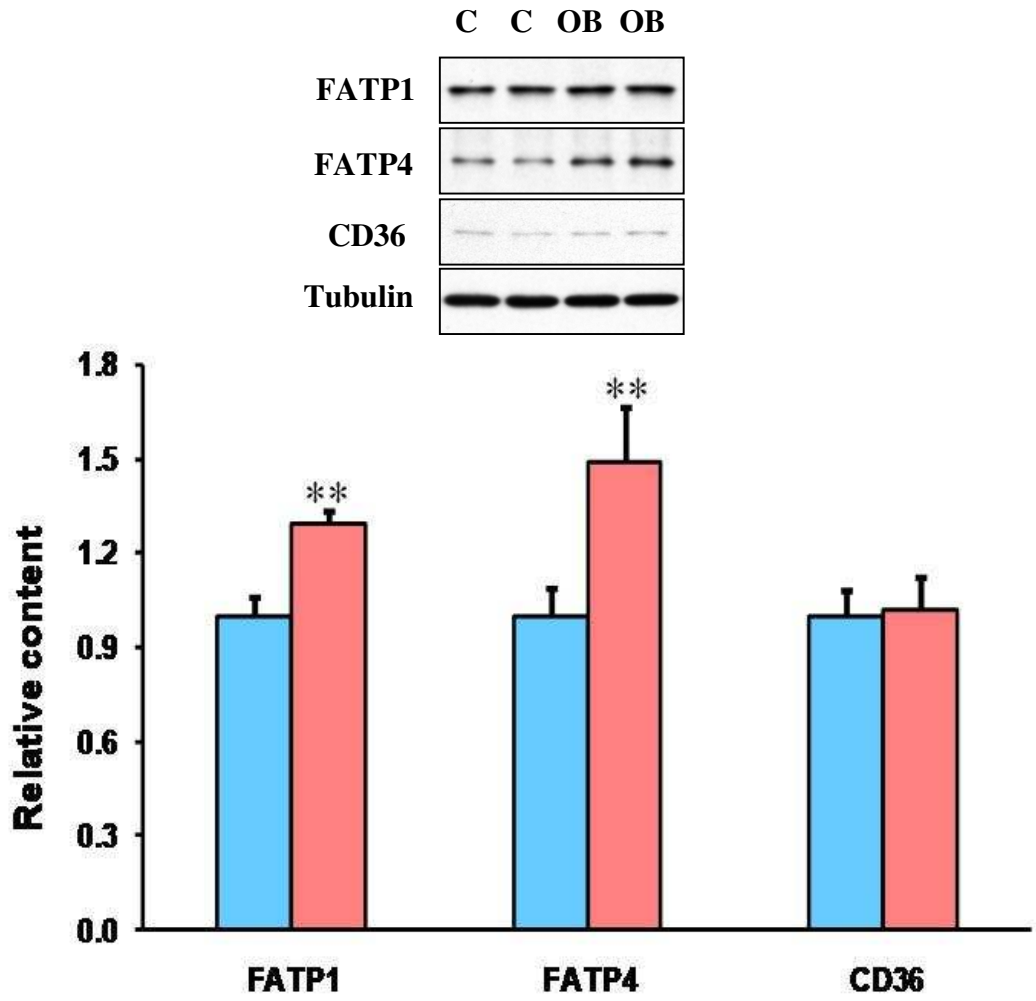
1) Placental growth and vascularization

2) Fetal organogenesis: fetal organs shown to be most affected by early gestational under nutrition include the pancreas.



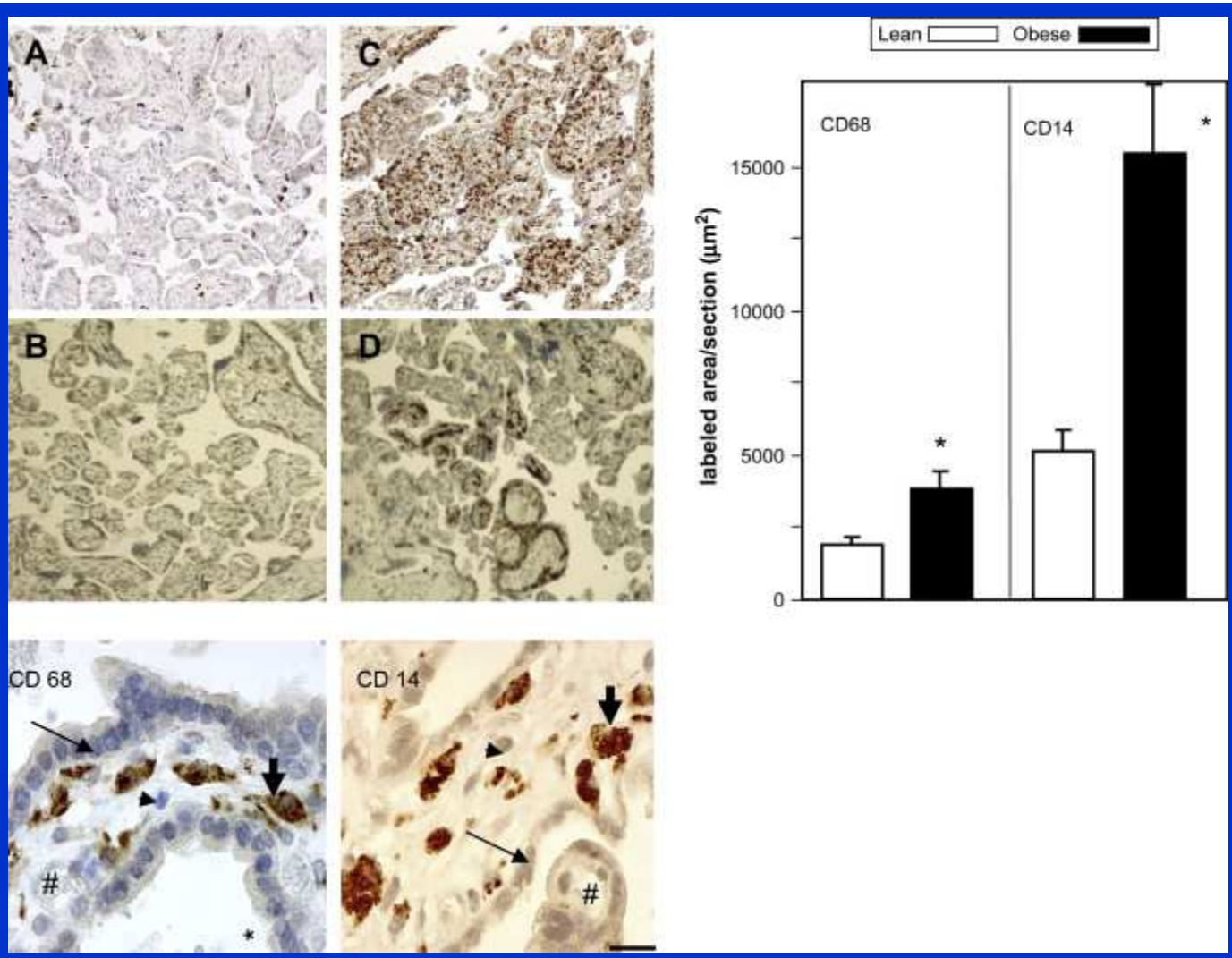
Vascularity in both CAR and COT tissues of OB and C ewes at d 75 of gestation

Relative Content of FATP1,FATP4 and CD36 protein in COT of Control and OB Ewes on Day 75 of Gestation



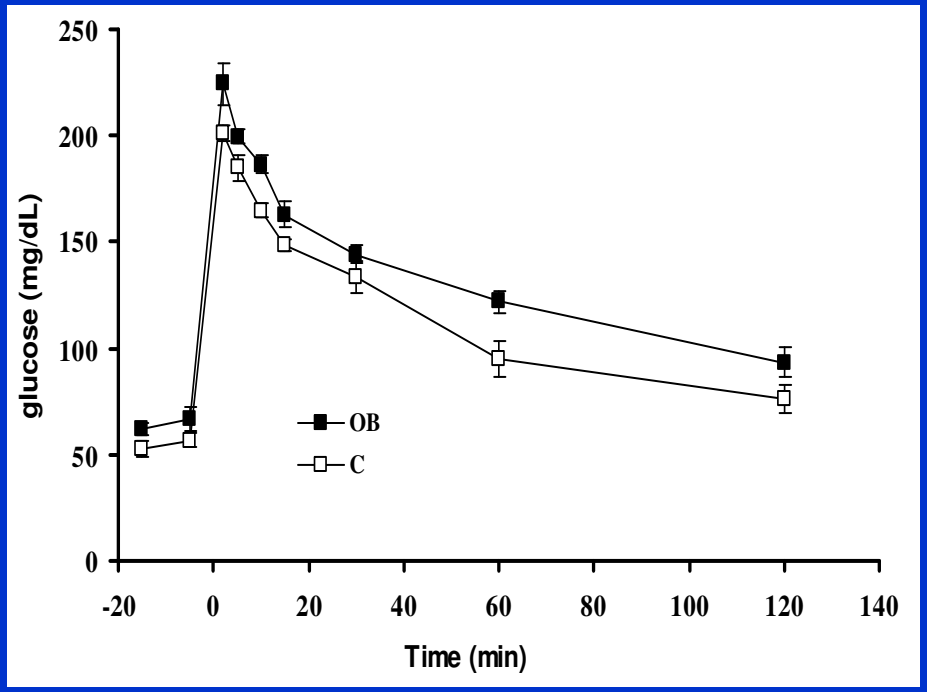
control fed ewes; obese over-nourished ewes:

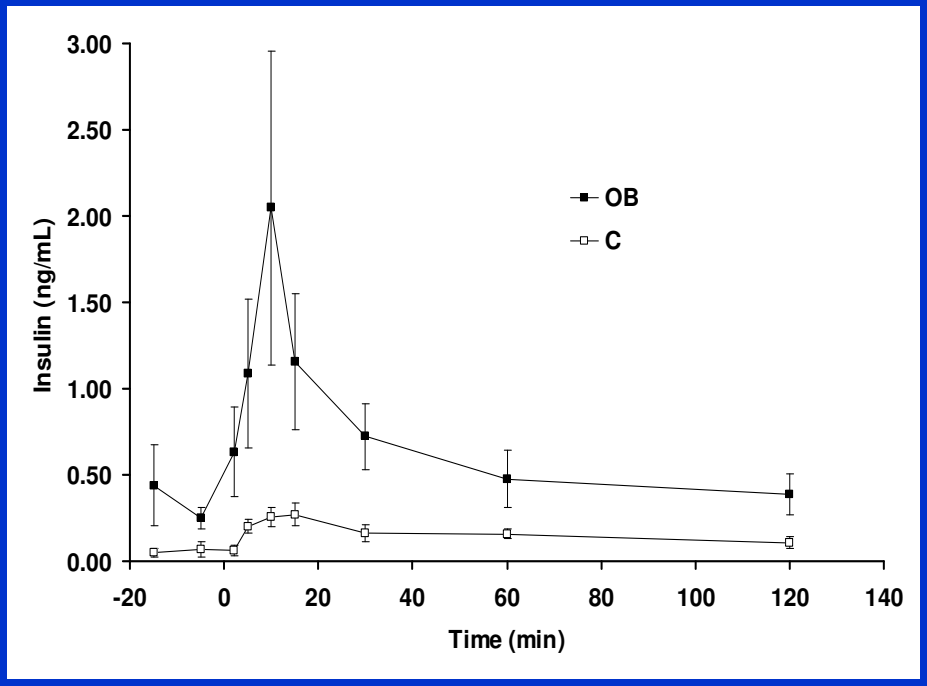
Mean ± SEM; **: $p<0.01$; n=5 in each group.



Placental macrophages in obese women. A: placental sections from a lean (pre-gravid BMI: 22.5) woman -rare Macrophage staining; an obese (pre-gravid BMI: 31.7) woman with increased numbers of macrophages (C) and (D). Right : Placental macrophage number. M ± SE. *: $p < 0.001$ obese vs lean. Lower panel: macrophages (thick arrows) in the villous stroma Thin arrow: syncytiotrophoblast nuclei, #: fetal blood space, *: maternal blood space. Scale 20 µm. **J.C. Challier et al Placenta 29 274-281**

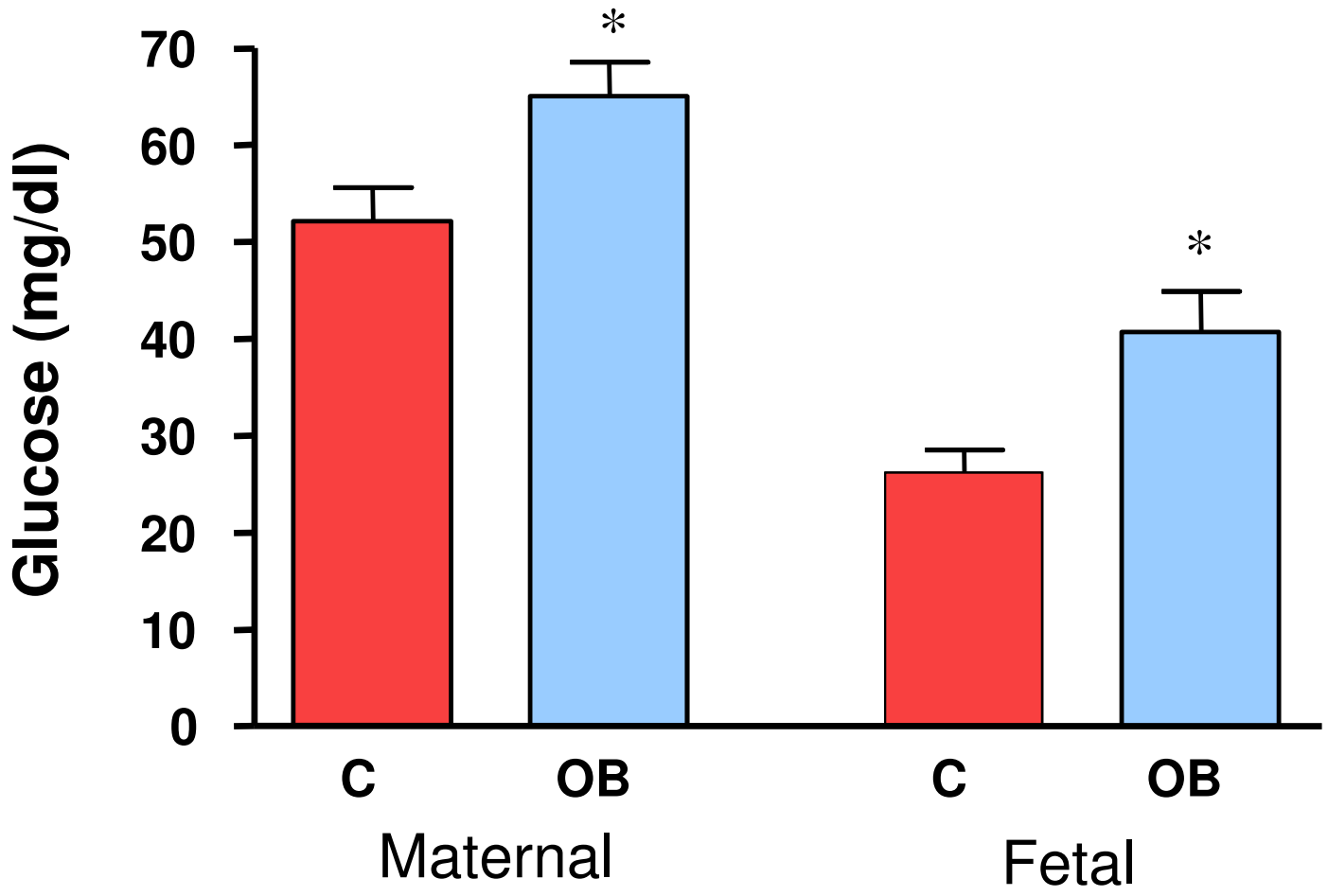
Concentration of Glucose and Insulin in Maternal Blood on 0.5 Gestation in the obese sheep model.





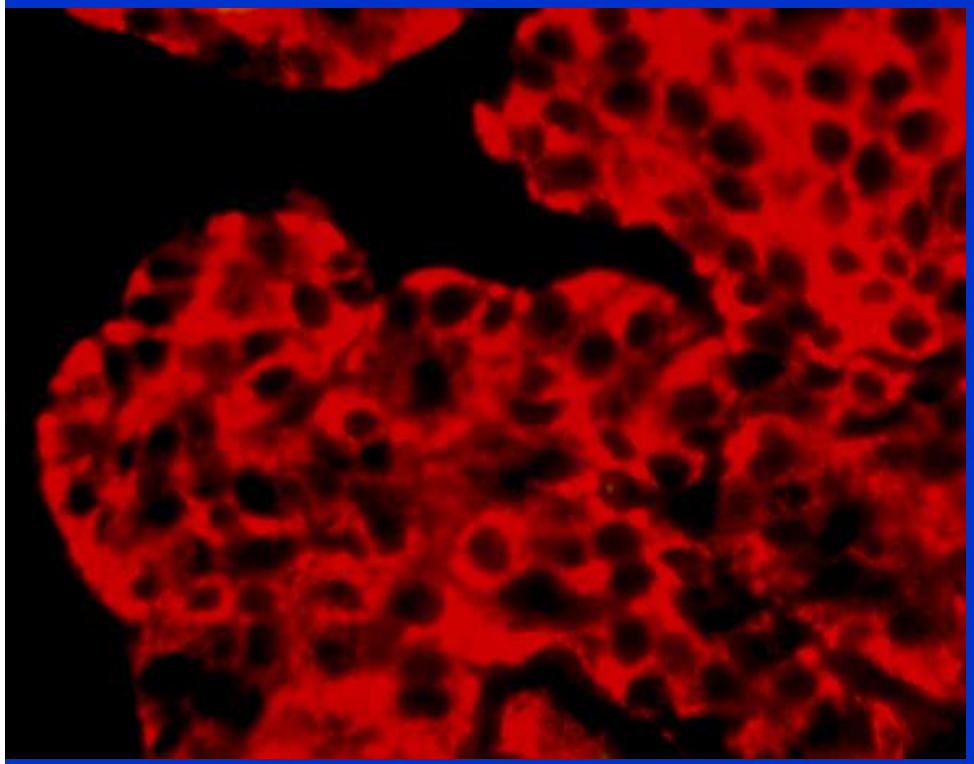
Area Under the Curve differs by dietary treatment ($P<0.05$)

Glucose Content in Both Maternal and Fetal Blood on D75 of Gestation

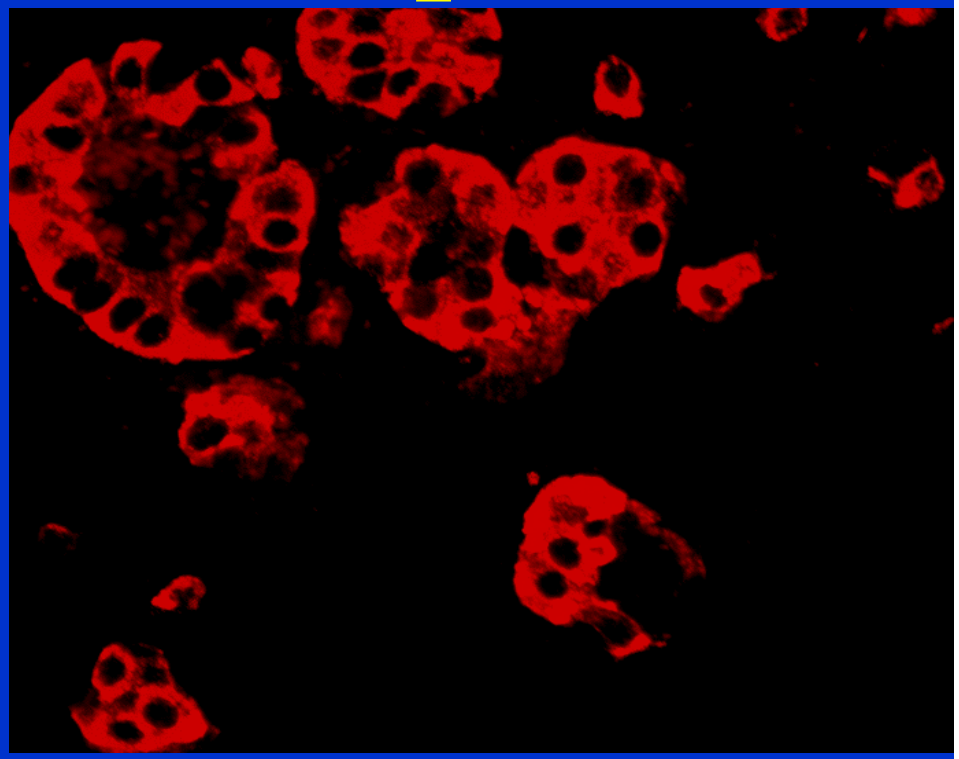


*Means ± SEM differ (P<0.05)

Beta cells in the pancreas of the fetal sheep

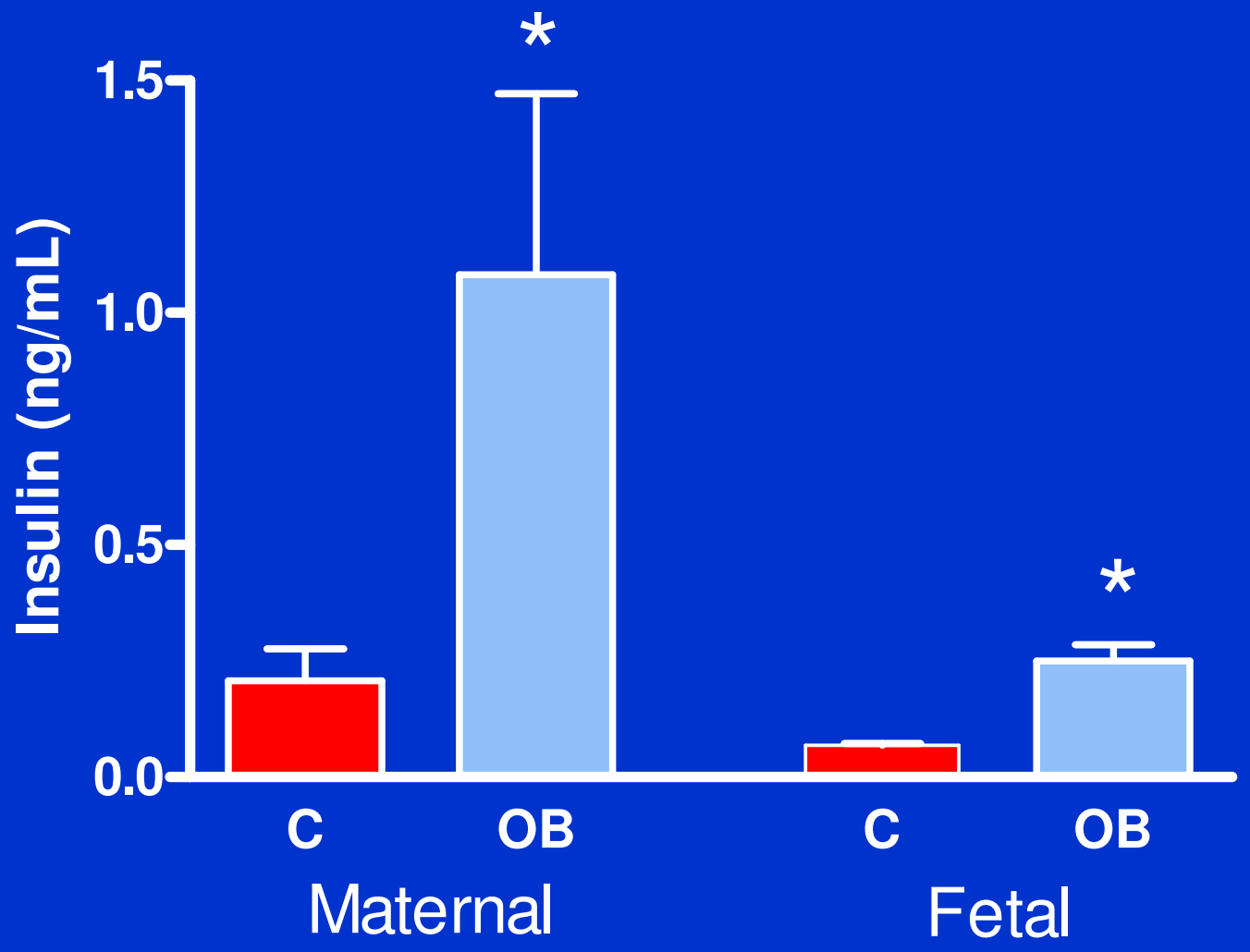


Fetal beta-cells in
- obese mother



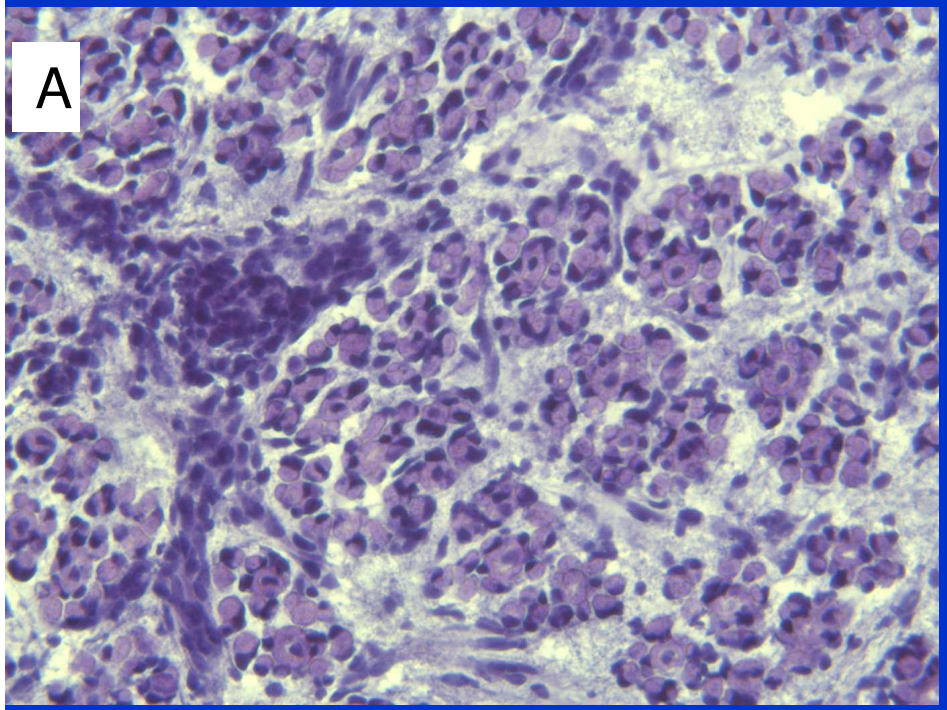
Fetal beta-cells in
control mother

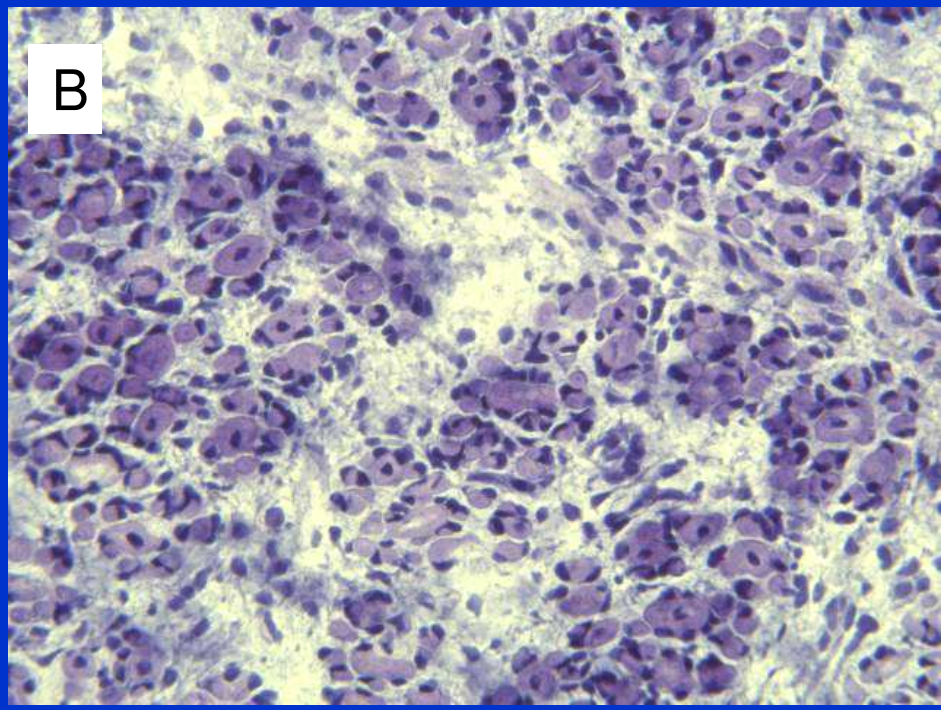
Insulin Content in Both Maternal and Fetal Blood on D75 of Gestation



*Means ± SEM differ (P<0.05)

Effect of obesogenic diet on fetal muscle histology

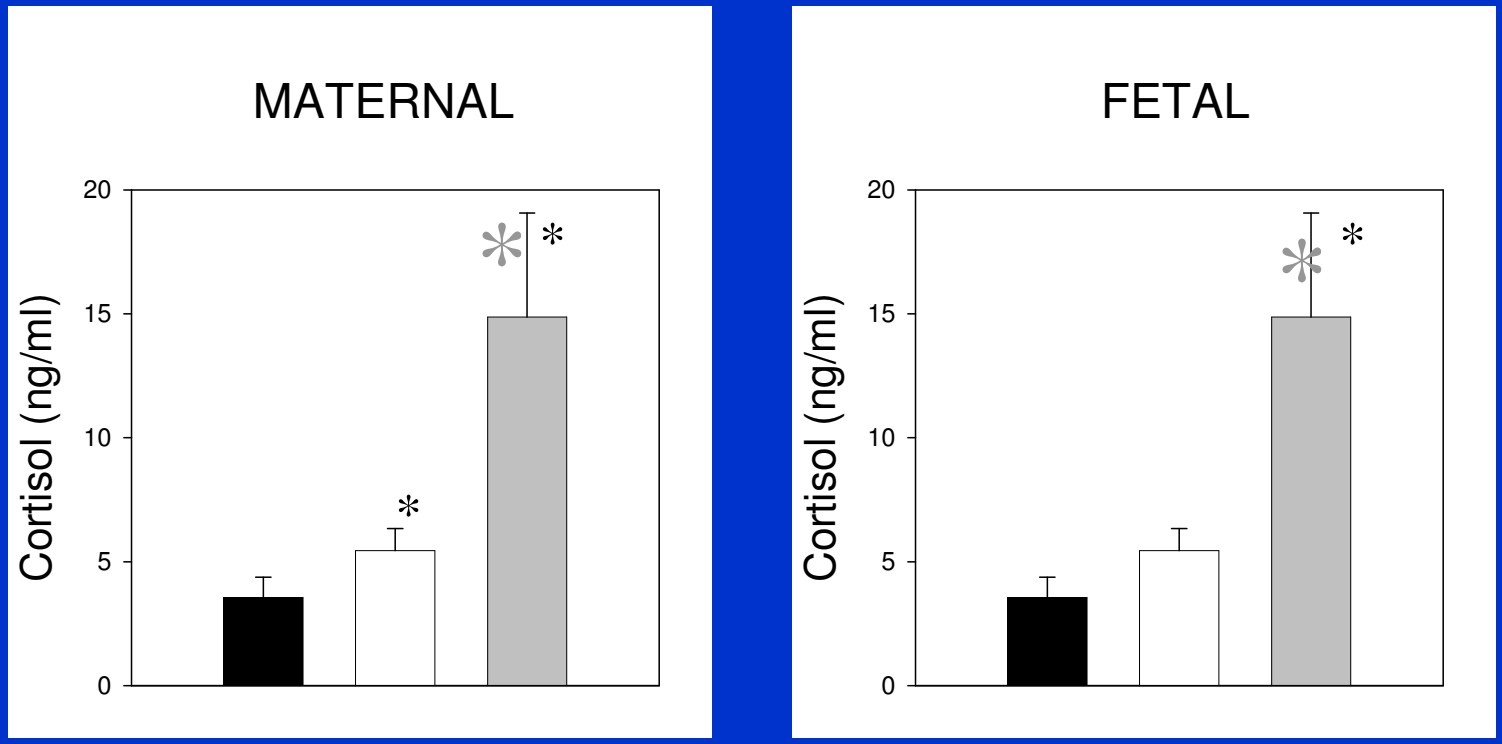




Con fetal muscle

OB fetal muscle

Fetal plasma cortisol at 0.5 G

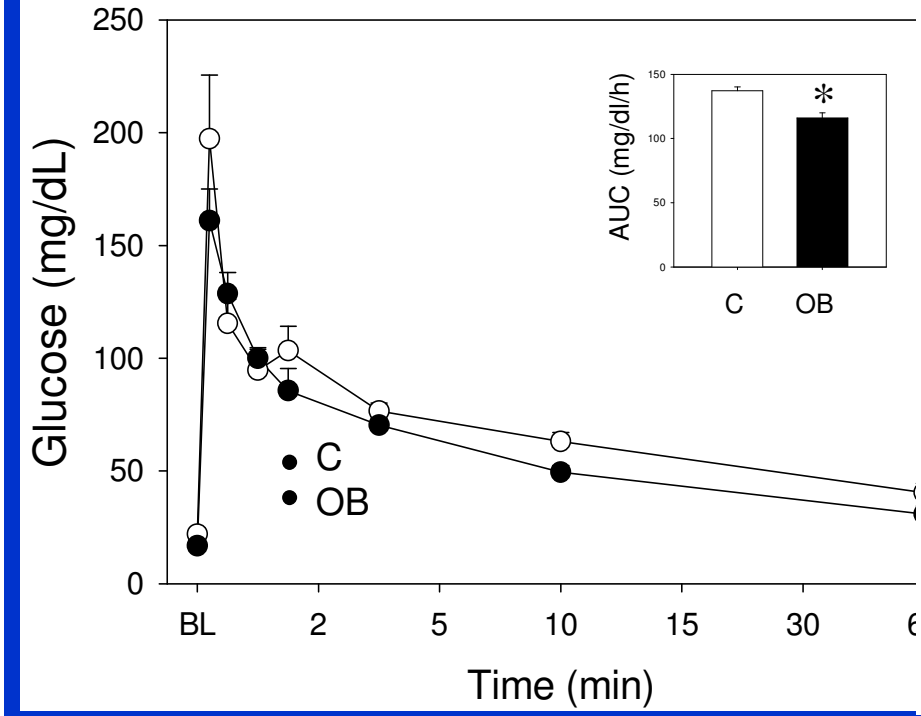


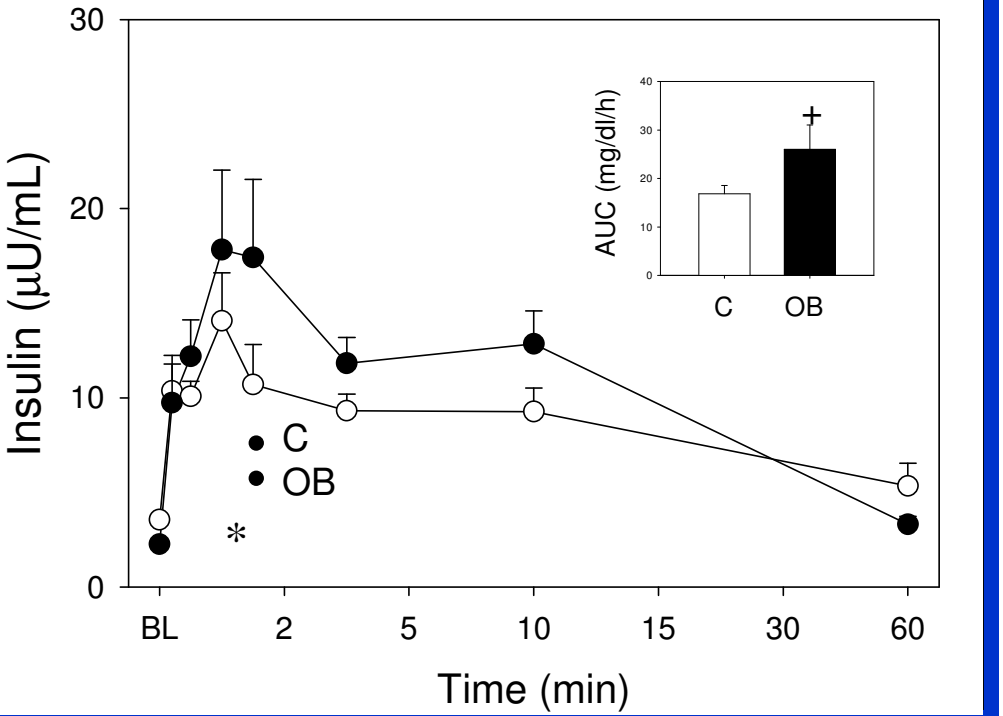
Cortisol in Control (CTR, n=6) maternal nutrient restricted (NR, n=6) and overfed (Fat, N=6) ewes and fetuses at 78 days of gestation. * p< 0.05 compared to CTR group.

Post natal data

We have evaluated glucose handling at two months of age.

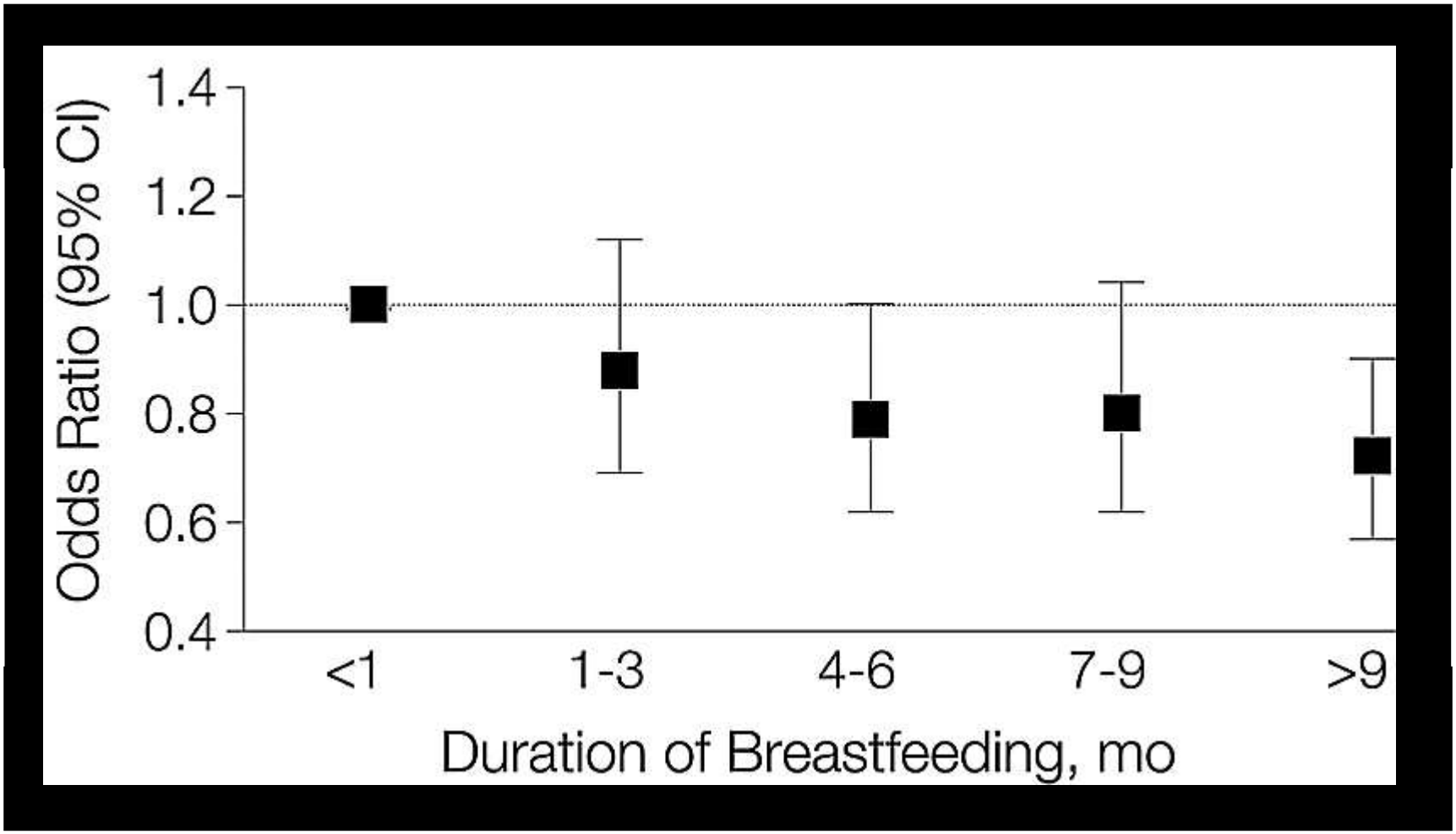
Concentration of Glucose and Insulin in Lambs at 2 Months of Age





Compared to Control group (C): *P<0.05; + p=0.07.

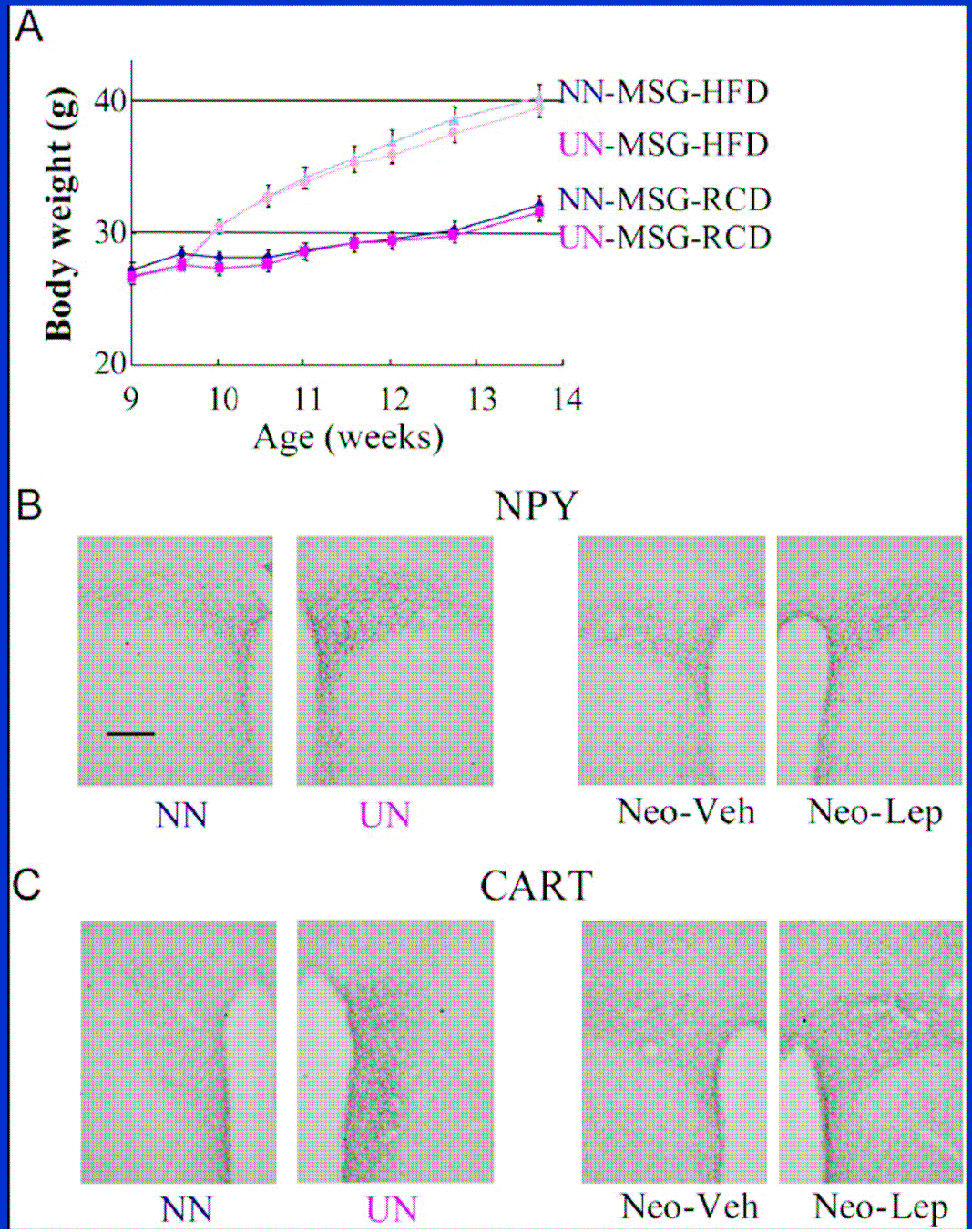
Risk of Overweight in Adolescence By Duration of Breastfeeding in Infancy



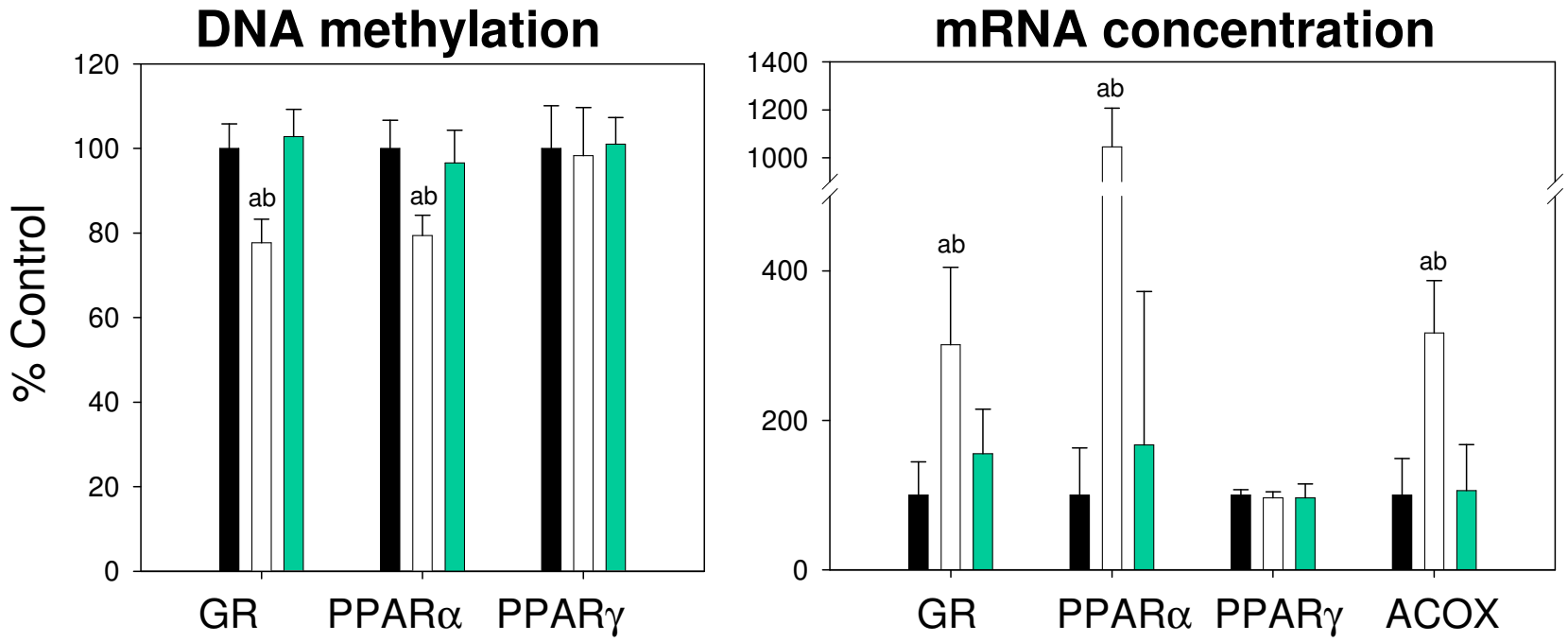
Gillman MW et al, JAMA 2001 285, 2461-2467

What are the possible mechanisms for the programming of a predisposition to obesity?

Yura et al Cell Metab. 2005 Jun;1(6):371-8.



Effects of maternal dietary protein restriction and folic acid supplementation during pregnancy in rats on gene promoter methylation and RNA expression in the offspring 34 d after birth



Diets: C 18% protein, 1mg/kg folic acid (■); R – 9% protein, 1 mg/kg folic acid (□); RF – 9% protein, 5mg/kg folic acid (■). Values are mean ± SD, n=10 offspring/ maternal dietary group. *P*< 0.05: a) vs C; b) vs RF.

Lillycrop K et al.

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Windows of Development

CC RR CR RC

At birth litters were adjusted to 12 pups/litter

Zambrano et al. (2005) Journal of Physiology 566: 225-236

Time line

Puberty

Adult life

day

	0	22	0	21	~90	~130	~270
	Gestation		Lactation		Growth		

CC	Control	Control	Control
RR	Restricted	Restricted	Control
CR	Control	Restricted	Control
RC	Restricted	Control	Control

Mothers

Pups

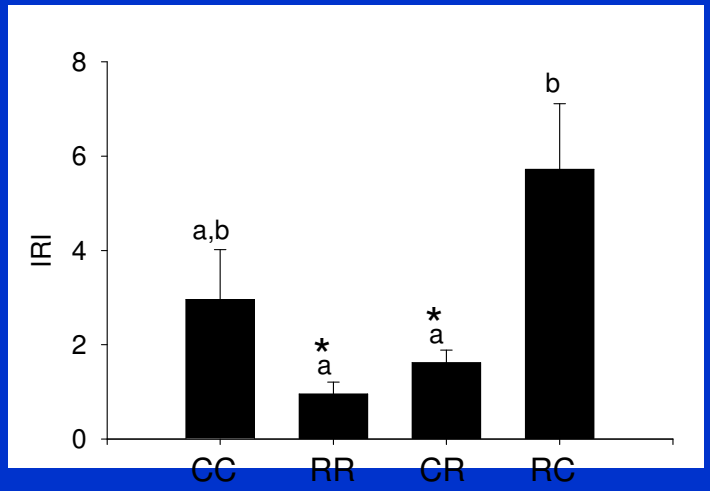
Programming of Obesity

22 month old female offspring from dams fed control (CC) and restricted (RC) diets

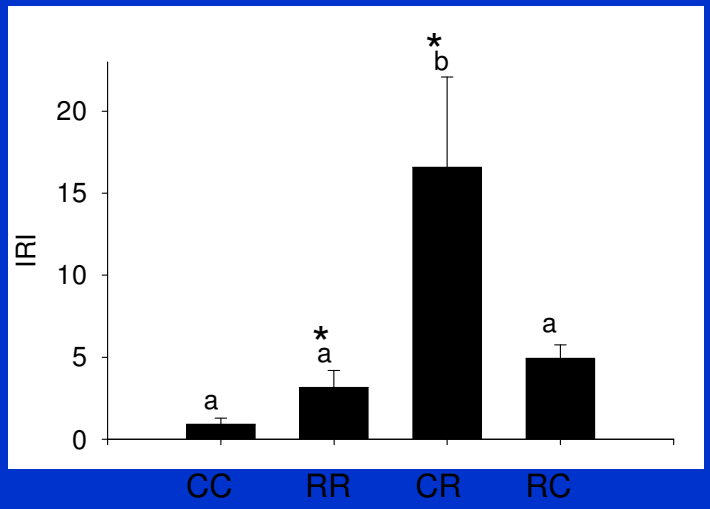
Zambrano et al. (2005) Journal of Physiology 566: 225-236

Transgenerational effects of maternal under nutrition on insulin resistance in granddaughters and grandsons.

Granddaughters



Grandsons



Insulin Resistance Index (IRI) in grand daughters and grandsons of rats fed either control (C - 20%) protein or restricted (R – 10%) protein diet during pregnancy (first letter) or lactation (second letter); mean ± SEM; n=12 -16.

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ACKNOWLEDGEMENTS

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- Elena Zambrano
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- Cun Li
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