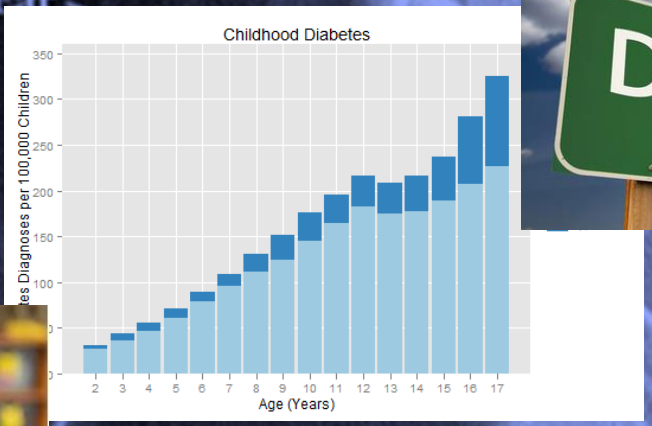
Maternal Obesity, Diabetes and Fetal Programming



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Mina Desai, Ph.D.
Department of Obstetrics & Gynecology
UCLA School of Medicine

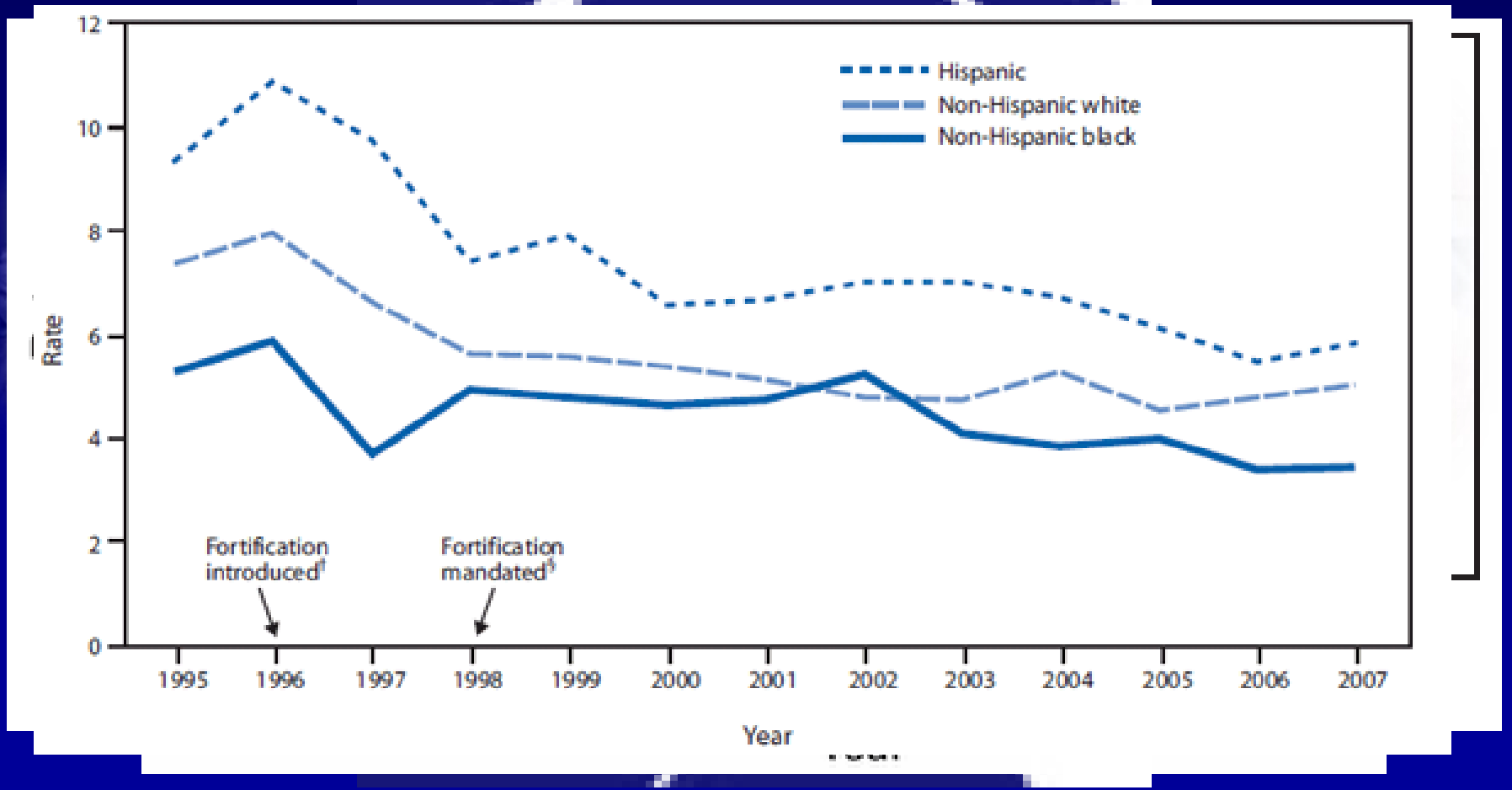
Outline: Fetal Programming

- Human epidemiology
- Animal studies
  - Phenotype
  - Mechanisms of Programming
    - Scope of the effect
    - Importance of the clinical interventions
    - Need for basic science advances

Prenatal Care Objectives Past, Present and Future

1940-1990: Prevent
1900-1950: Prevention of Maternal Mortality
1960-2010: Prevention of Birth Defects

Present and Future: Optimize Offspring Health



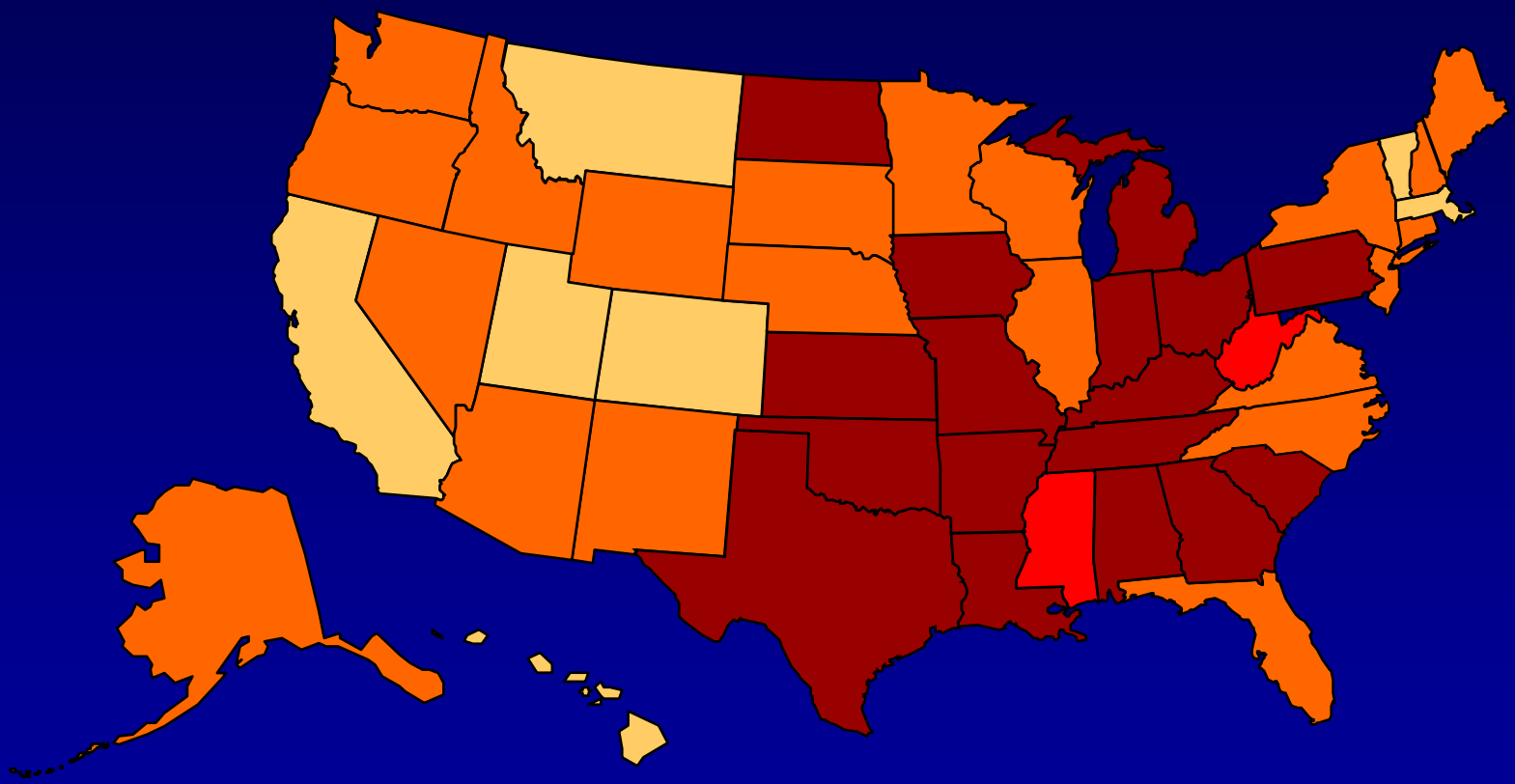
Metabolic Syndrome

- **Traits:**
  - Obesity
  - Hypertension
  - Type 2 diabetes mellitus
  - Dyslipidemia
- **Mortality:** Leading cause of death in the United States

- **Obesity:** U.S. adults 65% overweight, 31% obese,
  Childhood obesity 20%
- **Hypertension:** 29% of U.S. population
- **Diabetes:** 27% of U.S. population

Obesity Trends* Among U.S. Adults

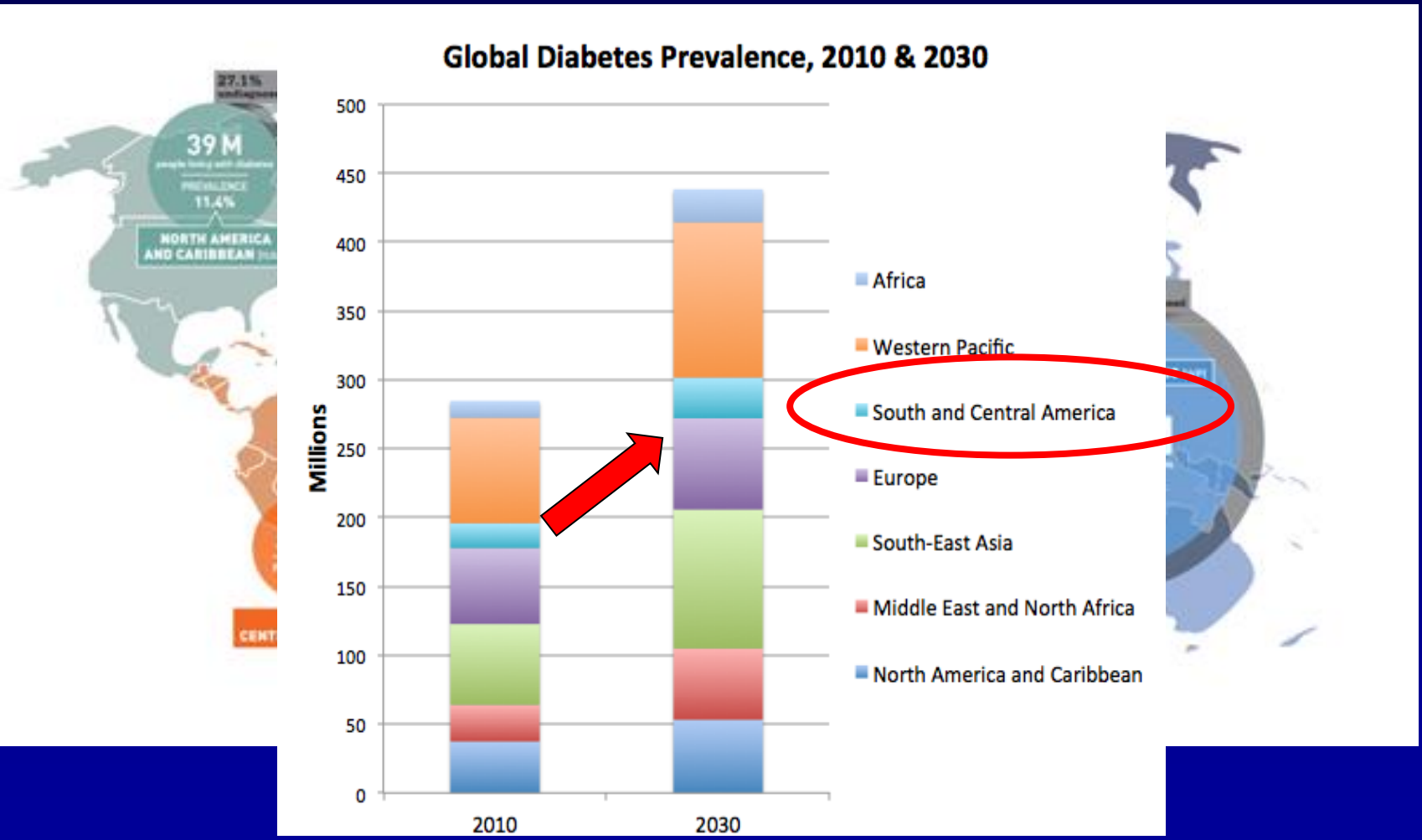
CDC, 2013



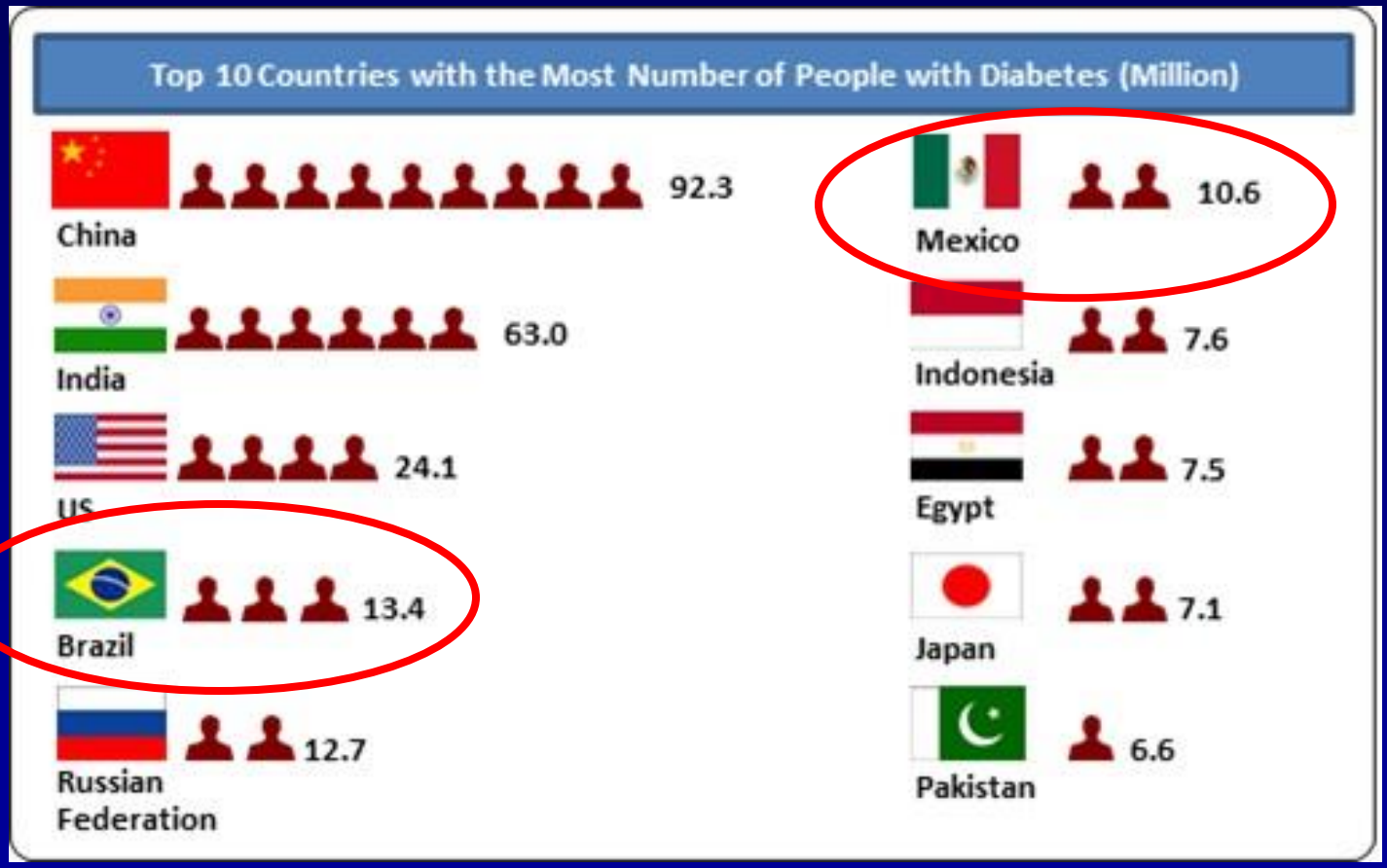
No Data | <10% | 10%–14% | 15%–19% | 20%–24% | 25%–29% | 30%-34% | ≥35%

Global Obesity

Global Diabetes

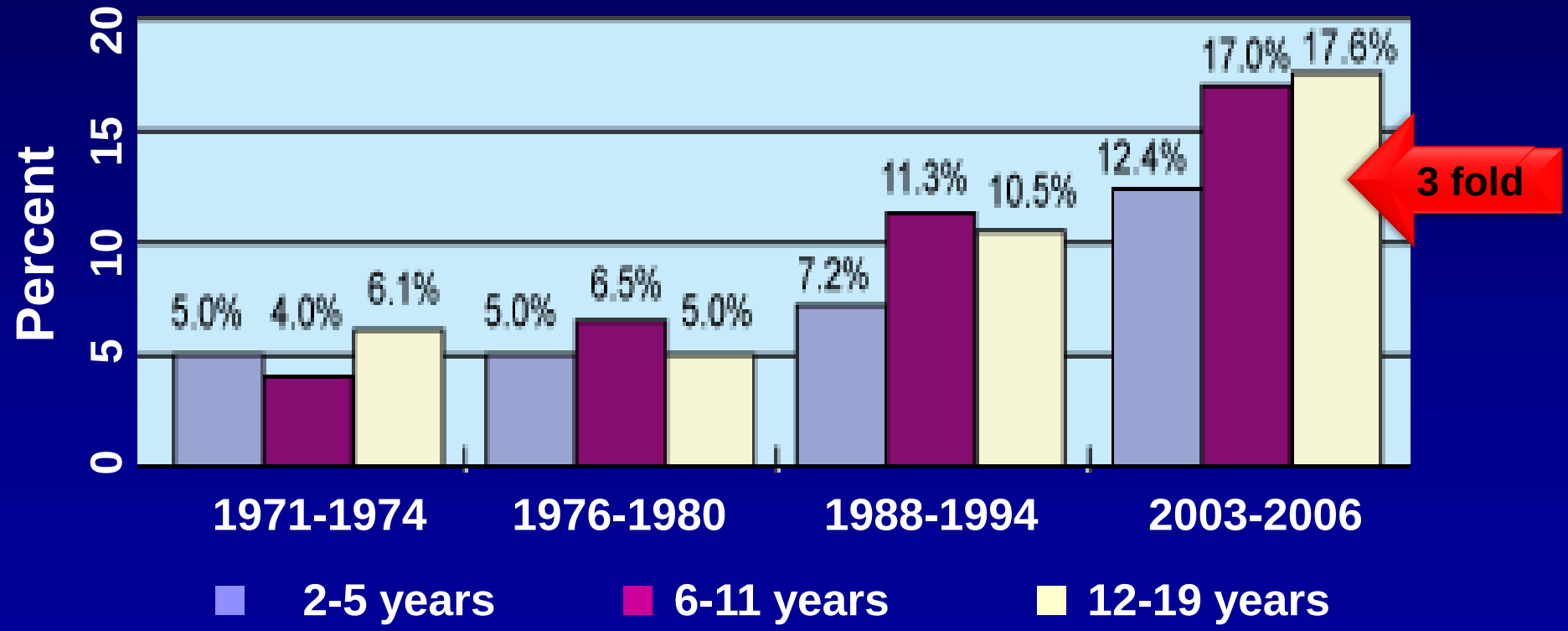


Top 10 Countries with Most Number of People with Diabetes



Prevalence of Obesity* Among U.S. Children and Adolescents (2 –19 Years)

National Health and Nutrition Examination Surveys



*Sex-and age-specific BMI ≥ 95th percentile based on the CDC growth charts

Child Overweight and Obesity

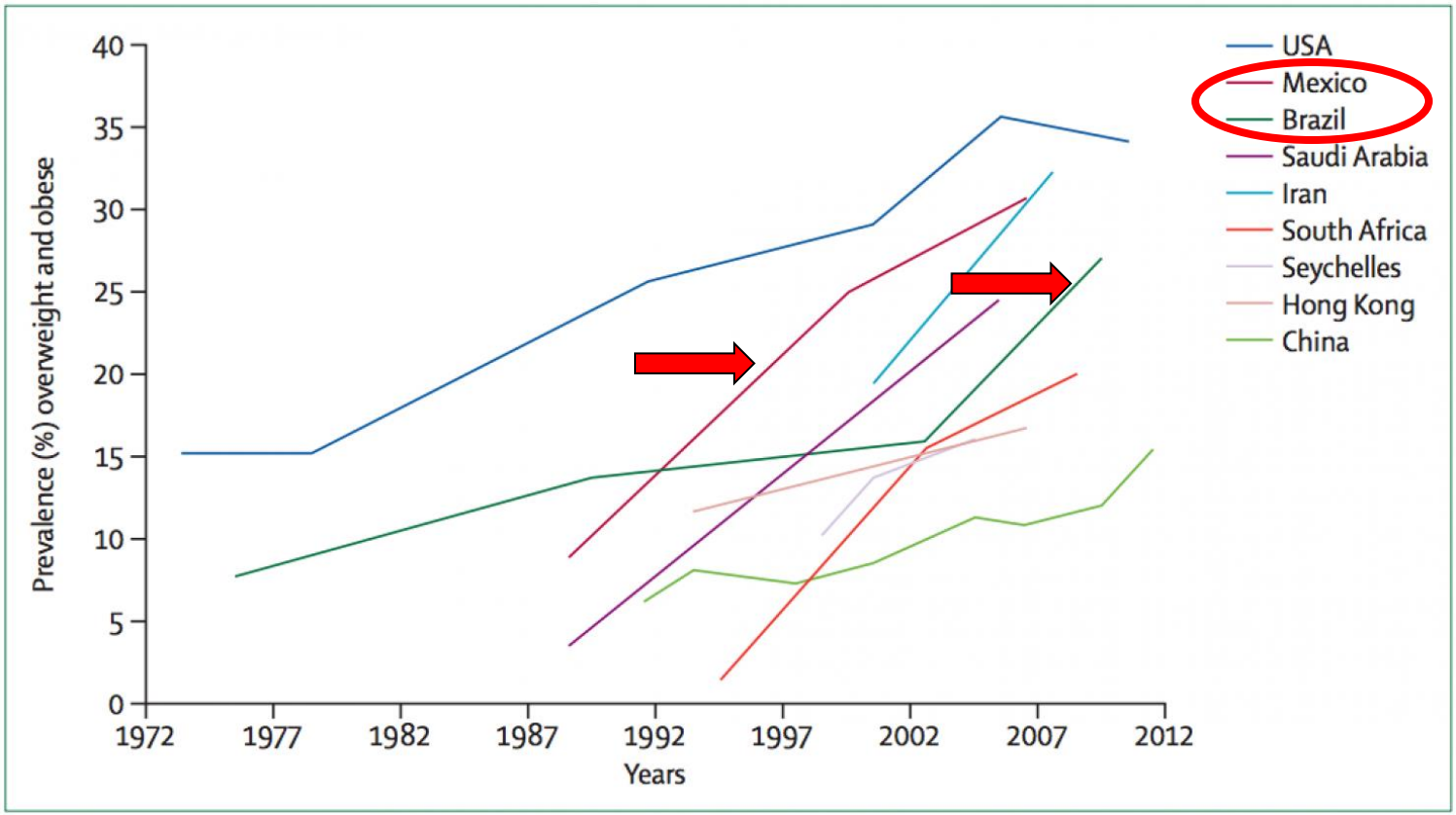
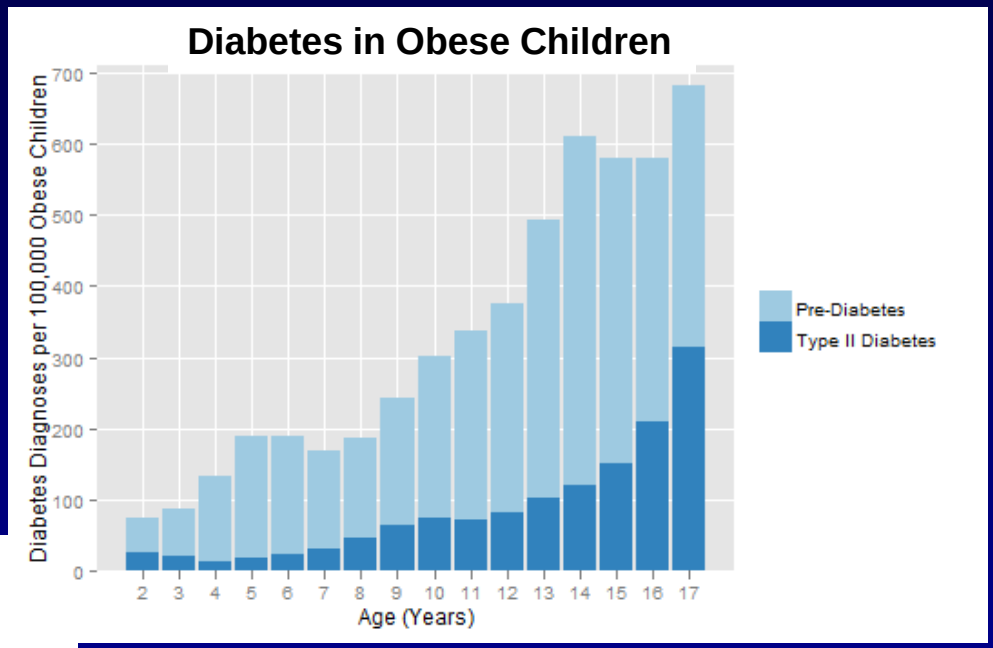


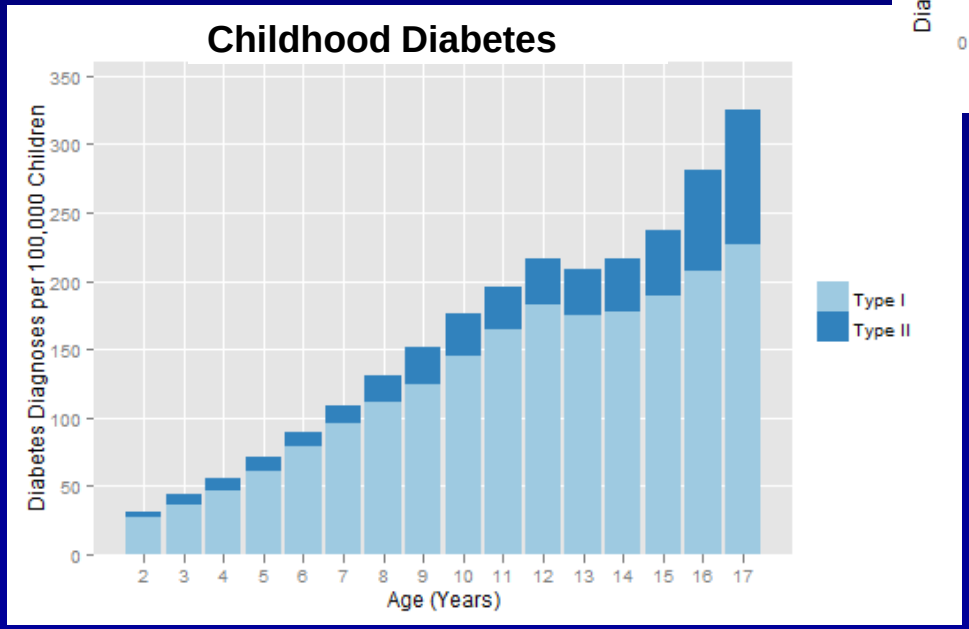
Figure 1: **Prevalence trends for child overweight and obesity in the USA and eight low-income and middle-income countries**

Source: World Obesity Federation, collated from published sources. Further details in appendix. Measurements of body-mass index are based on professionally measured heights and weights.

Childhood Diabetes

2 fold rate of diabetes in obese children





Etiology of Obesity/Diabetes

- Food Availability
  High Fat Diets

- Reduced Energy
  Expenditure

- Propensity for
  Obesity/Diabetes

- Developmental
  Programming

Developmental Programming

Fetal Nutrition, Stress
Environmental Toxins

Altered cell number
and differentiation

Modified gene expression
altered function

Propensity for Obesity/Diabetes

Barker Hypothesis
Developmental Programming

Small for Gestational Age (SGA) and/or Low Birth Weight (LBW) human newborns

- Paradoxical increased risk of hypertension, obesity, and diabetes as adult

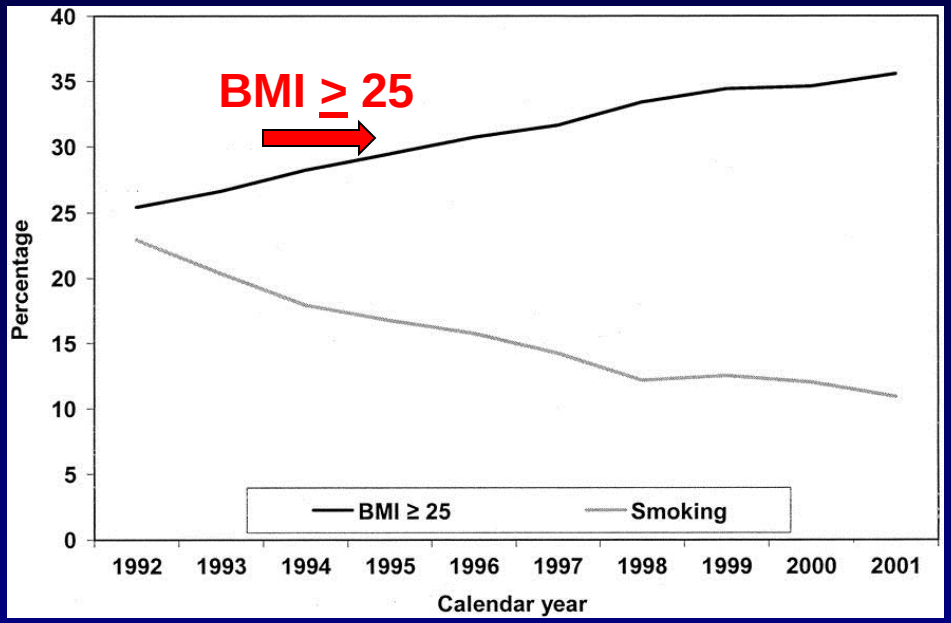
Barker Hypothesis
Developmental Programming

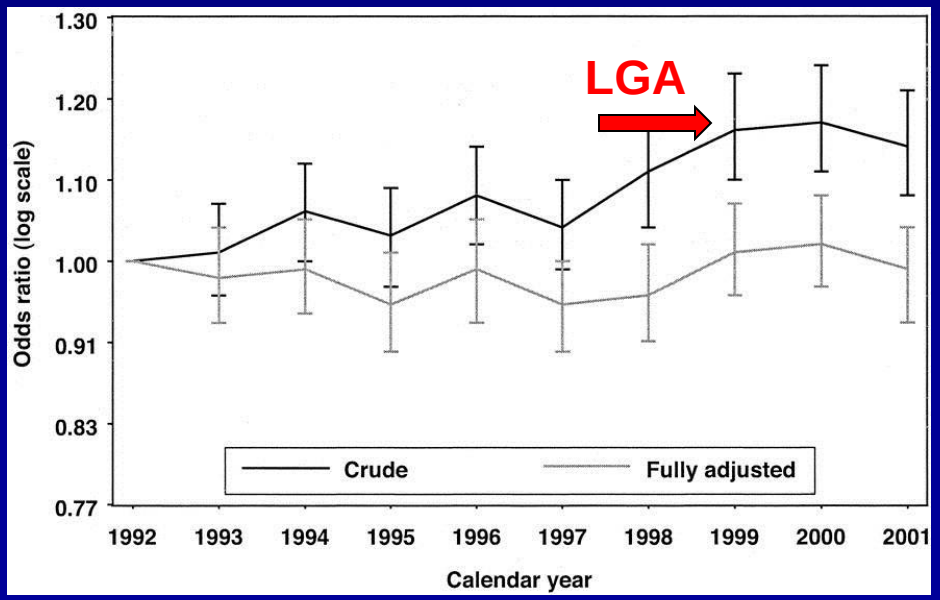
Large for Gestational Age (LGA) and/or

Macrosomic human newborns

Markedly increased risk of hypertension, obesity, and diabetes as adult

Maternal Overweight: Increased LGA Births

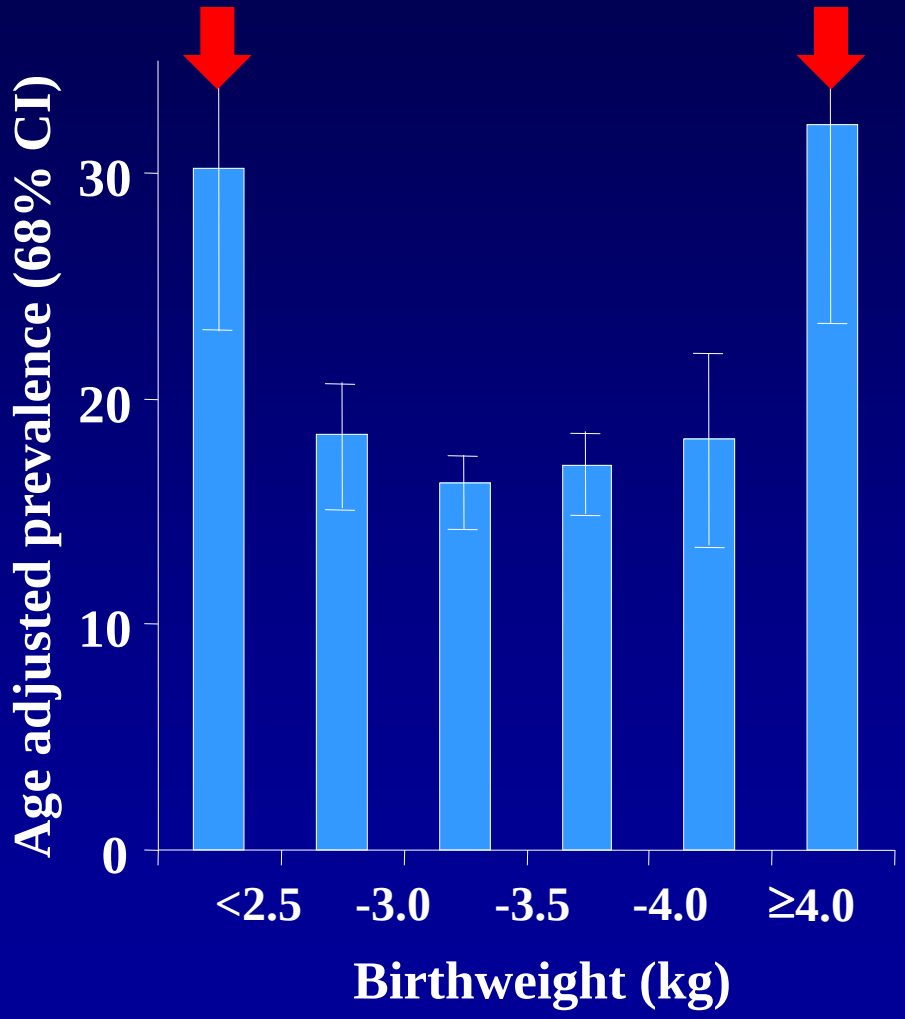




Obstetrics & Gynecology:
October 2004, Surkan, PJ et al .

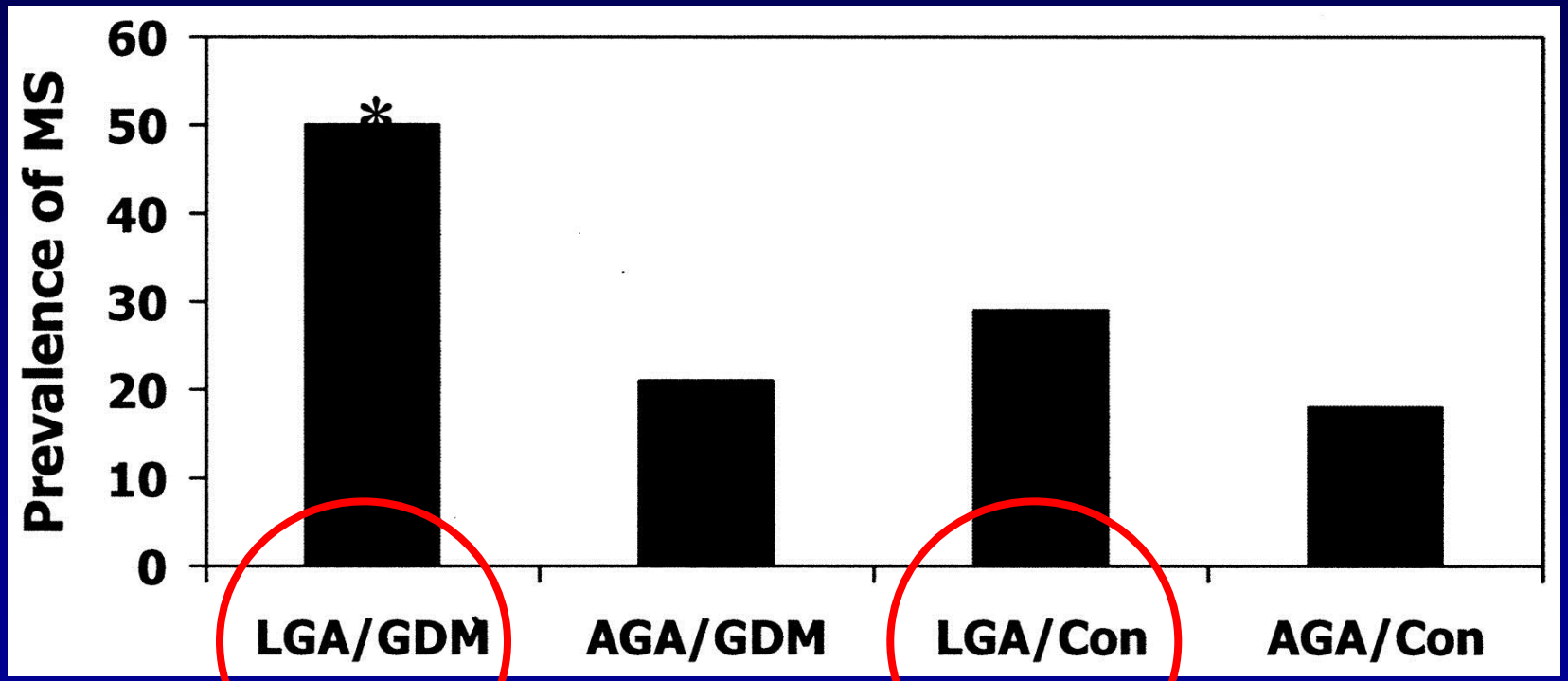
Birth Weight and Type 2 Diabetes

1179 Pima Indians aged 20-39 years



McCance DR et al BMJ 1994;308:942

Prevalence of Metabolic Syndrome among children grouped according to birth weight and maternal diabetes



Charlotte M. Boney et al. Pediatrics 2005;115:e290-e296

Birth Weight and Adult Diseases
Epidemiological Studies

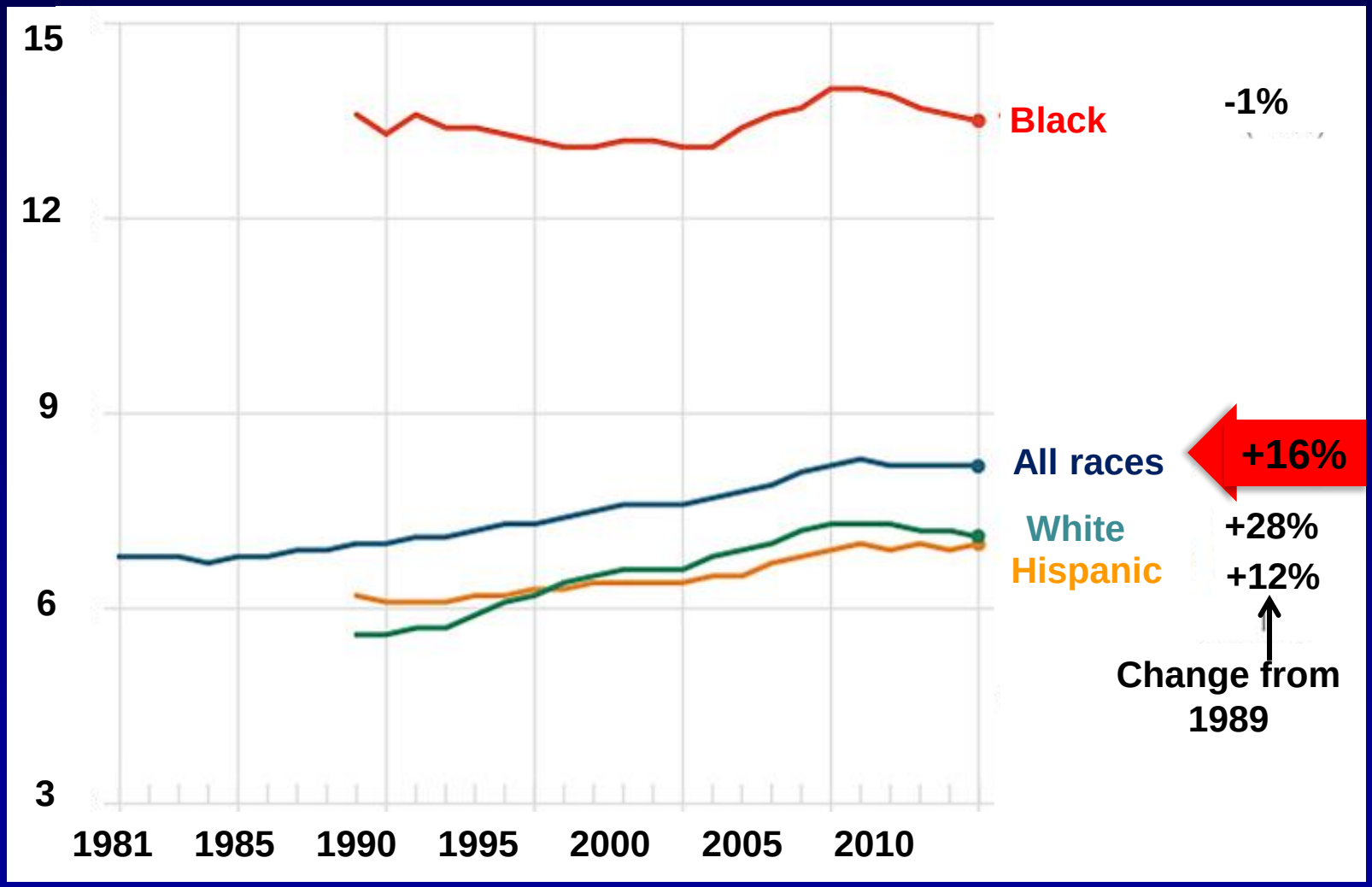
- Obesity
- Diabetes
- Cardiovascular Disease
- Hypertension
- Lipids
- Fatty Liver
- Immuno-compromise, Allergies
- Addiction, Substance abuse

Models of Fetal Programming

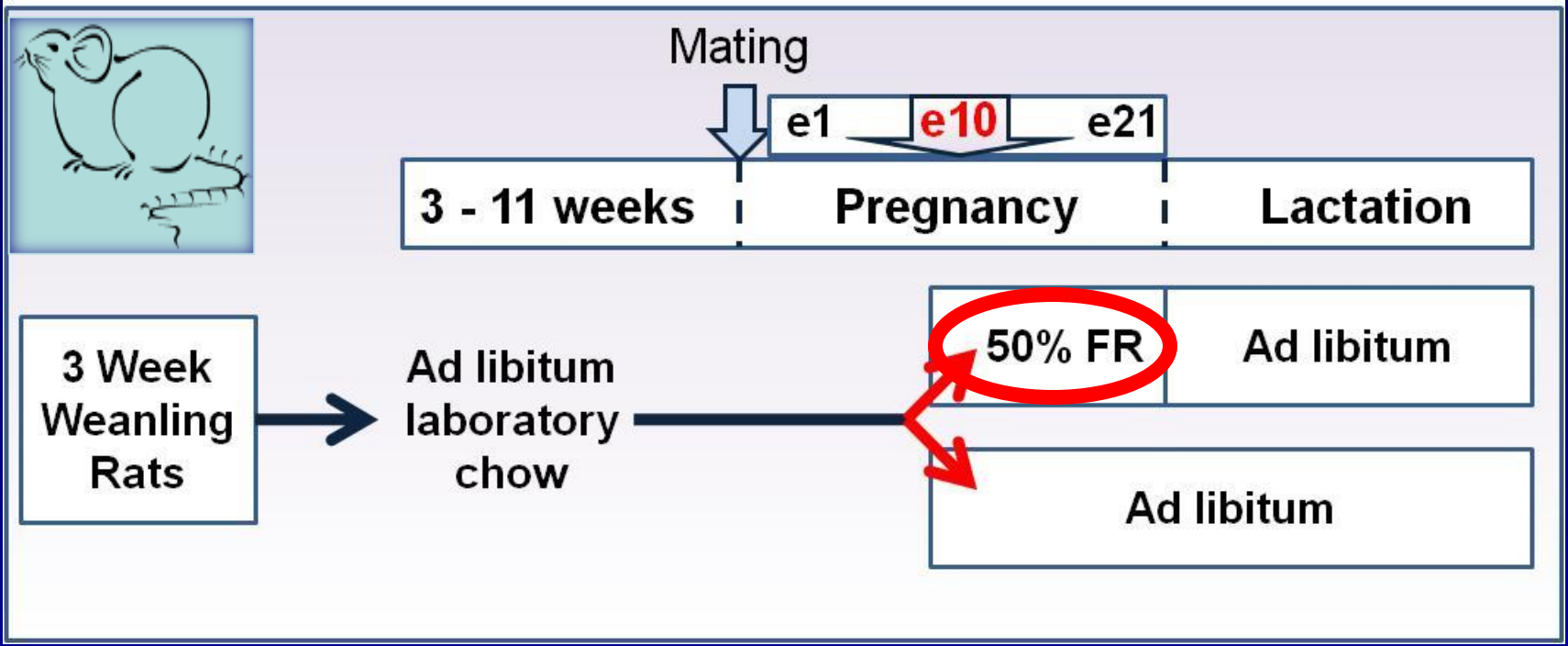
- Low Birth Weight
- Maternal Obesity

- Phenotype
- Mechanisms of Appetite and Adipose Programming

Low Birth Weight Trends in USA



Model of Intrauterine Growth Restriction (IUGR)
Maternal Food Restriction (FR)

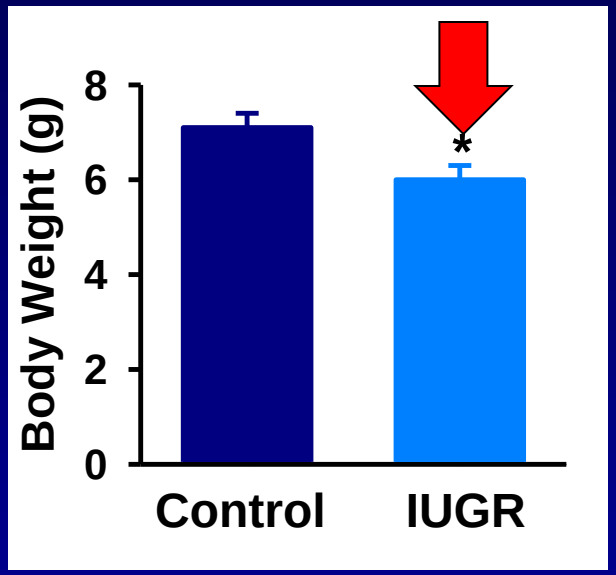


OFFSPRING

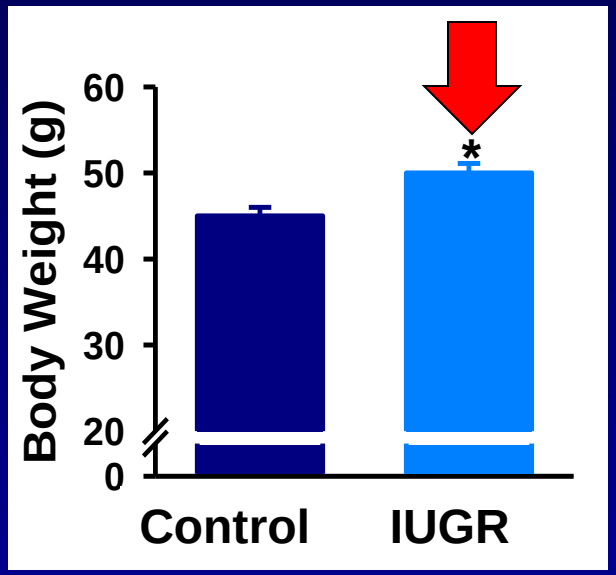
- **Litter size:** Culled to 4 males and 4 females at birth
- **Nursing:** All pups cross-fostered to ad libitum fed Control dams until p21
- **Weaning:** At p21 to ad Libitum food and water

Body Weight of Male Offspring

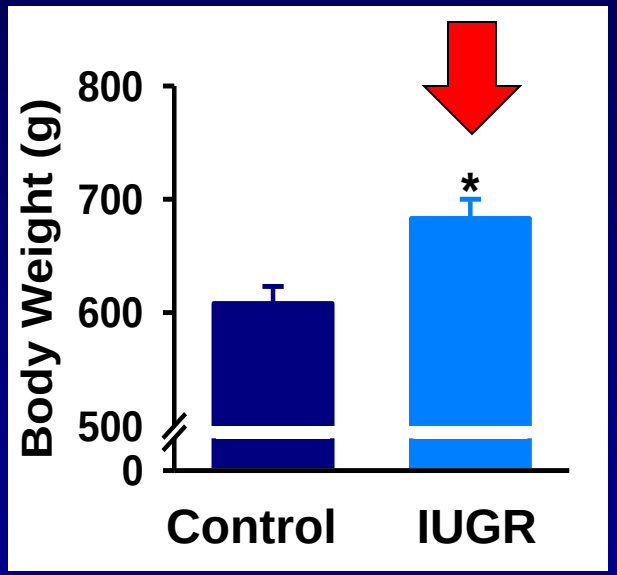
1 Day



3 Weeks



9 Months



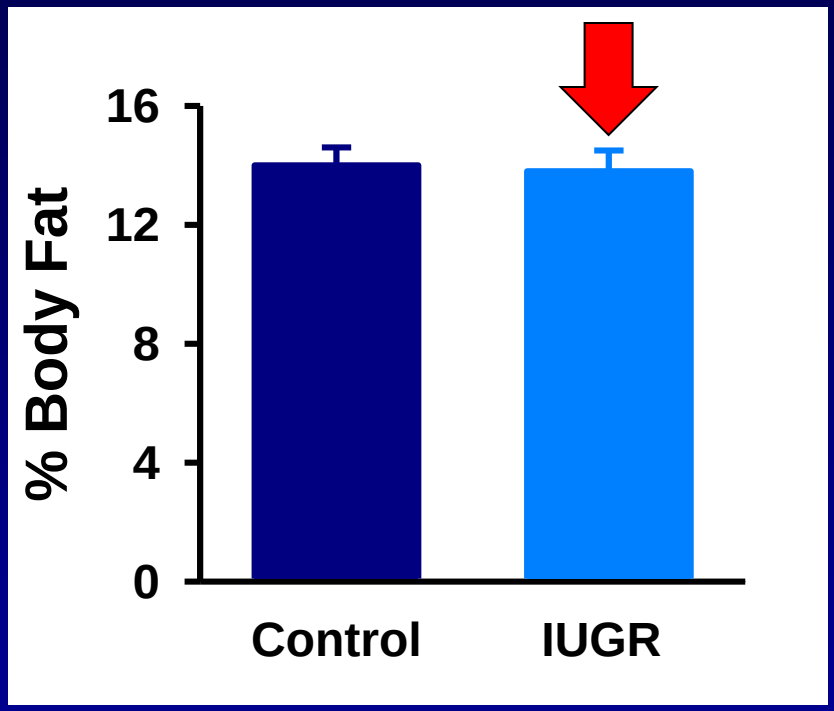
Rapid Catch-up Growth

Mean ± SE; * p < 0.01

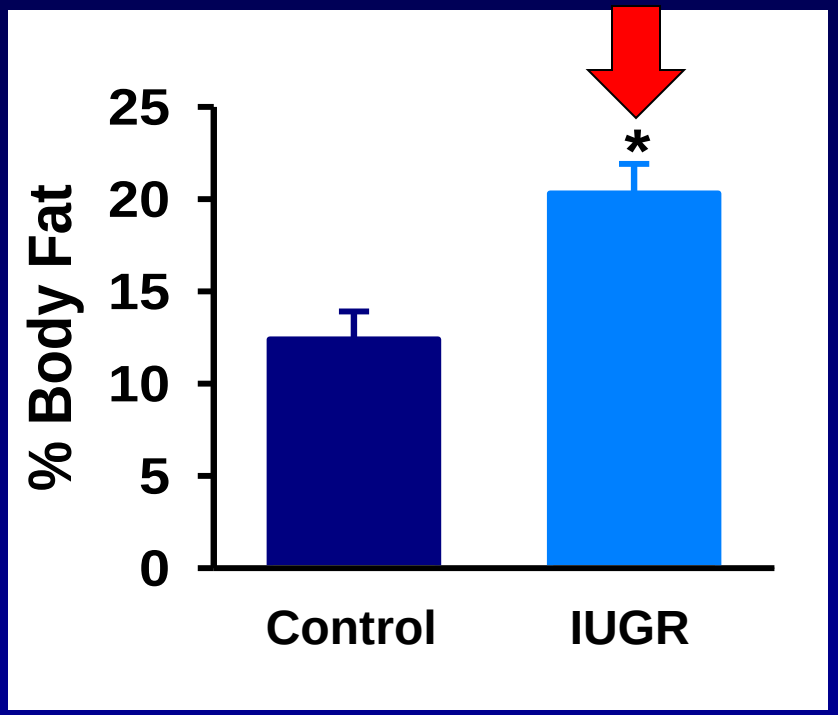
Desai et al, Am J Physiol, 2005

% Body Fat of Male Offspring

3 Weeks



9 Months

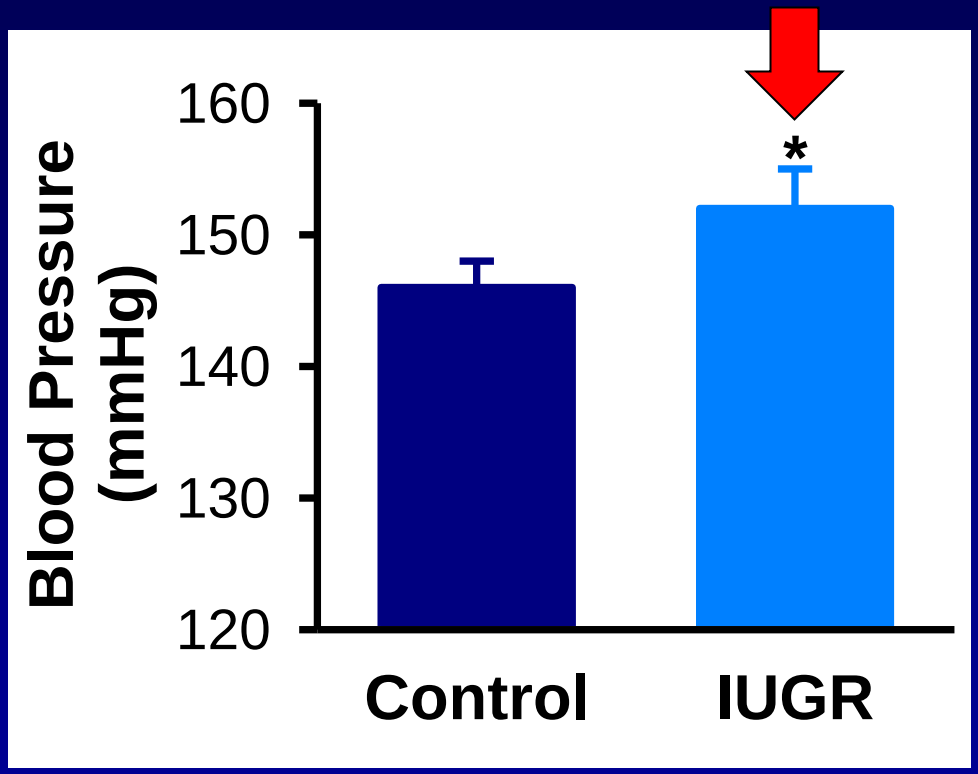


Adult Obesity

Mean ± SE; * p < 0.001

Desai et al, Am J Physiol, 2005

Systolic Blood Pressure
3 Month Obese Adult Males

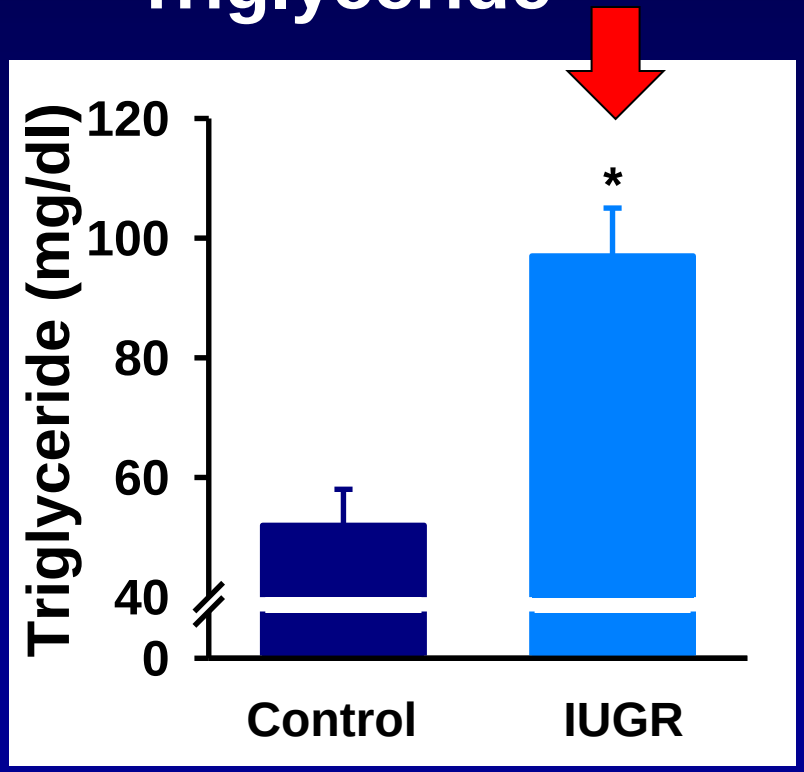


Hypertension

*** P < 0.05 vs. Control**

Lipid Profile
IUGR Obese Adult Males

Triglyceride

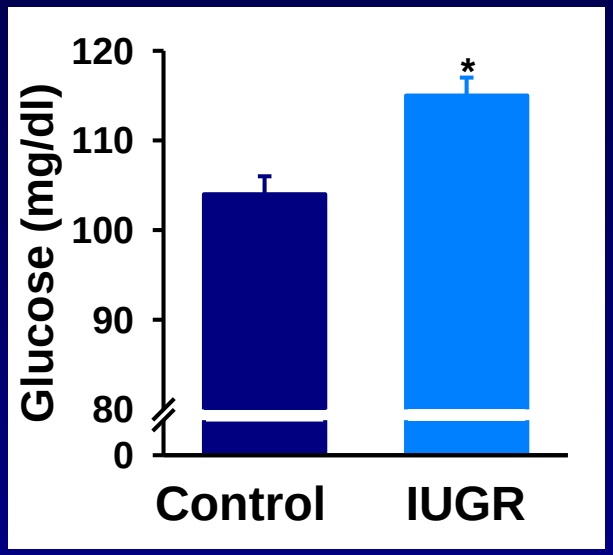


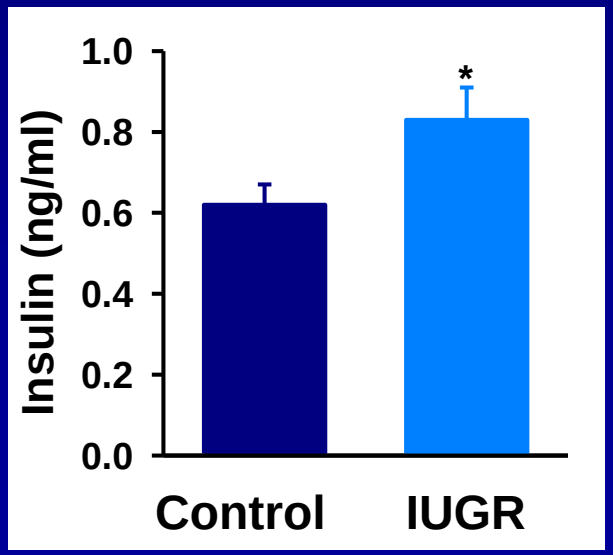
Hypertriglyceridemia

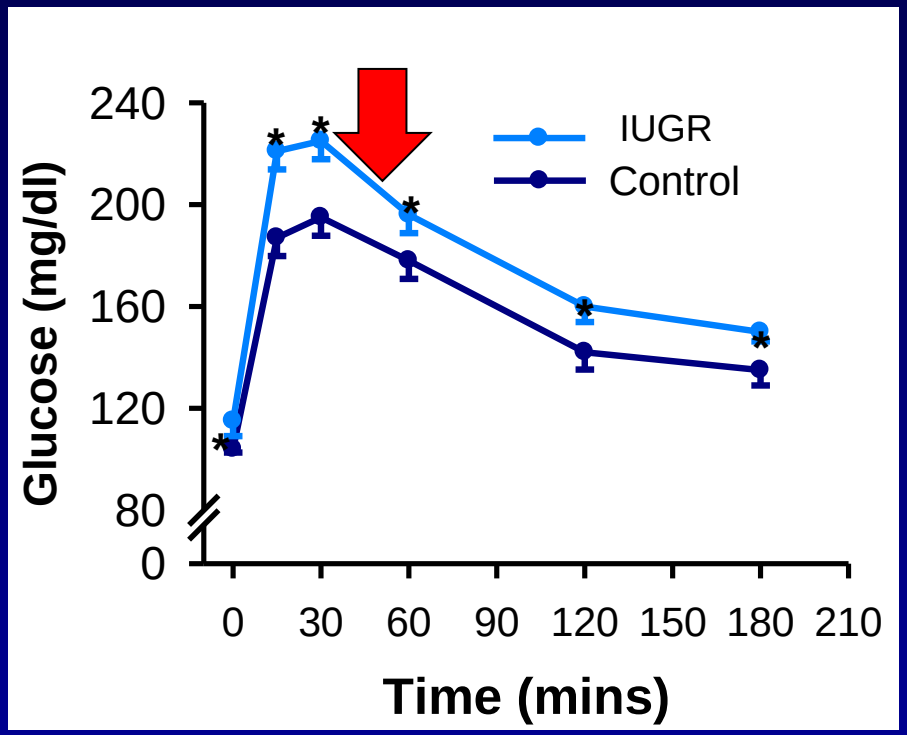
Mean ± SE; * p < 0.001

Desai et al, Am J Obstet Gynecol, 2007

Diabetes: Insulin Resistance IUGR Adult Males



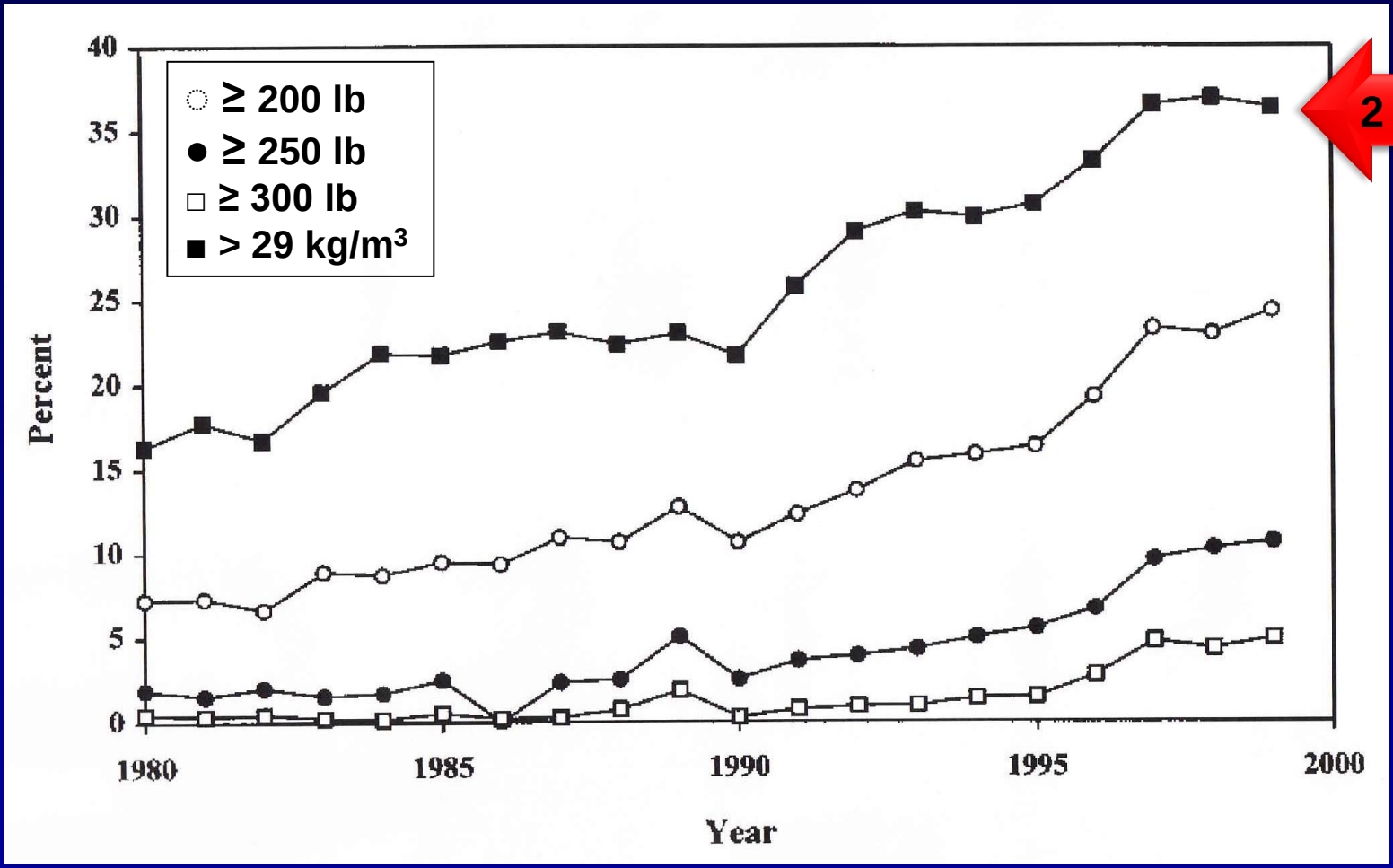




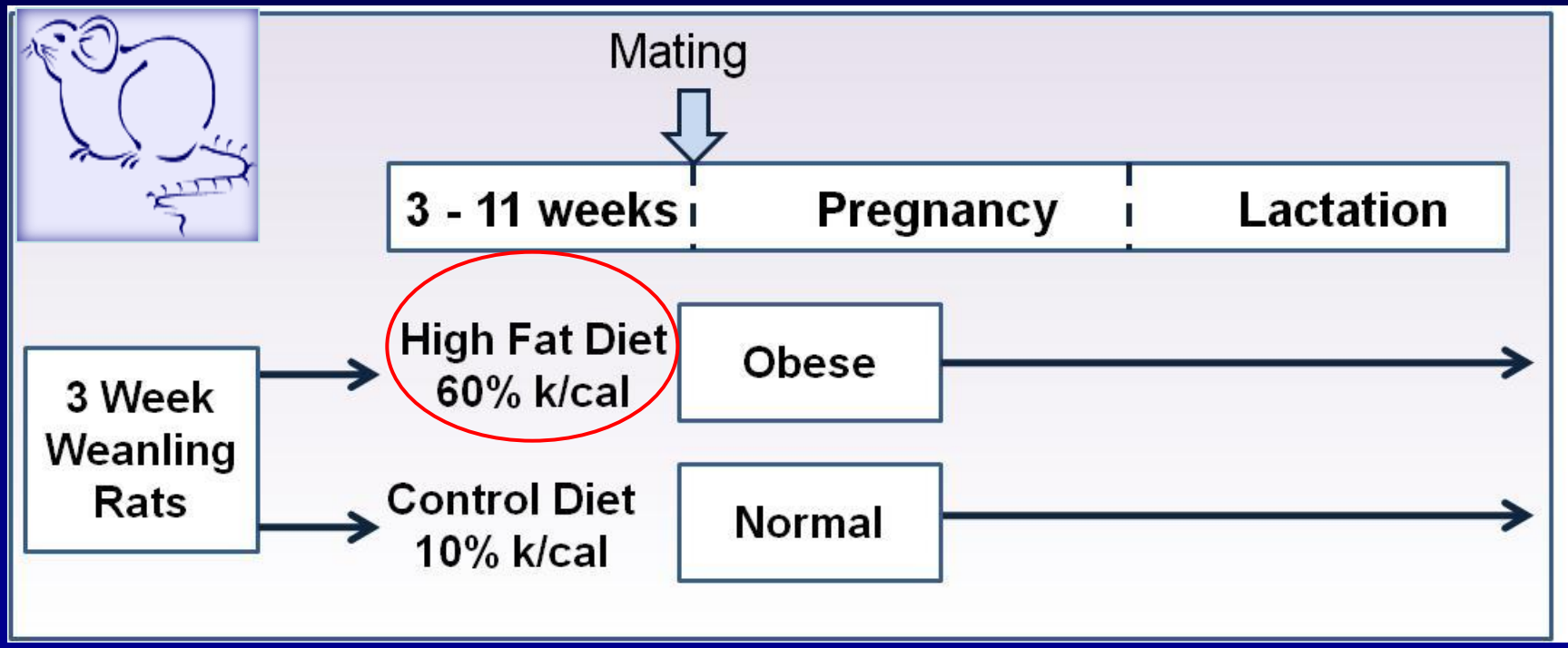
Insulin Resistance

Desai et al, Am J Obstet Gynecol, 2007

First Prenatal Visit: Prevalence of Maternal Obesity



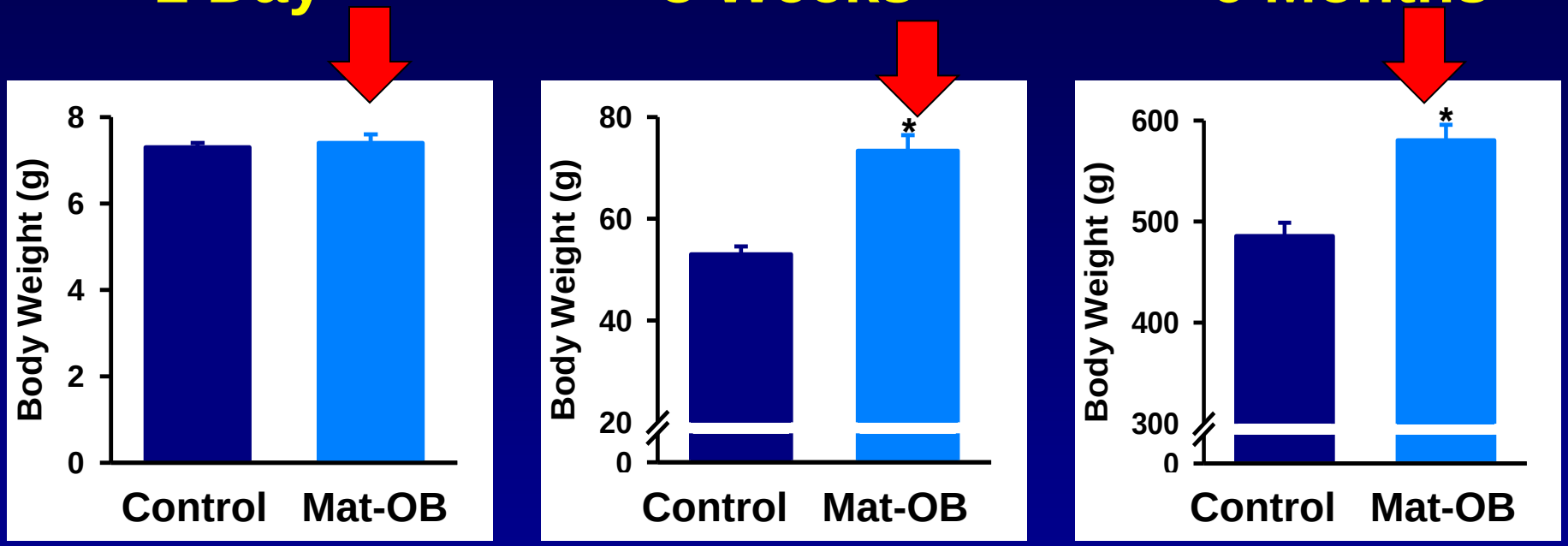
Model of Maternal Obesity
High Fat Diet



OFFSPRING

- **Litter size:** Culled to 4 males and 4 females at birth
- **Nursing:** All pups nursed by same dams until p21
- **Weaning:** At p21 to ad Libitum food and water

Body Weight of Male Offspring

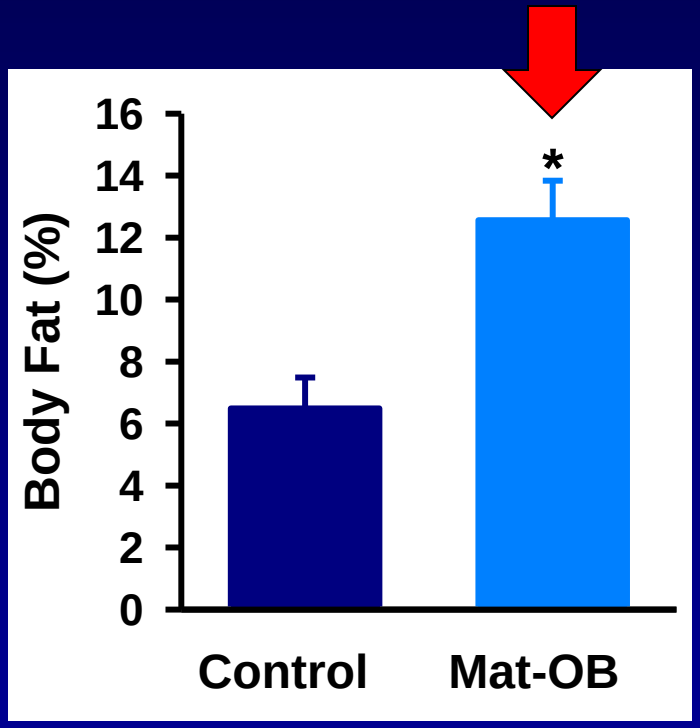


Accelerated Growth During Nursing

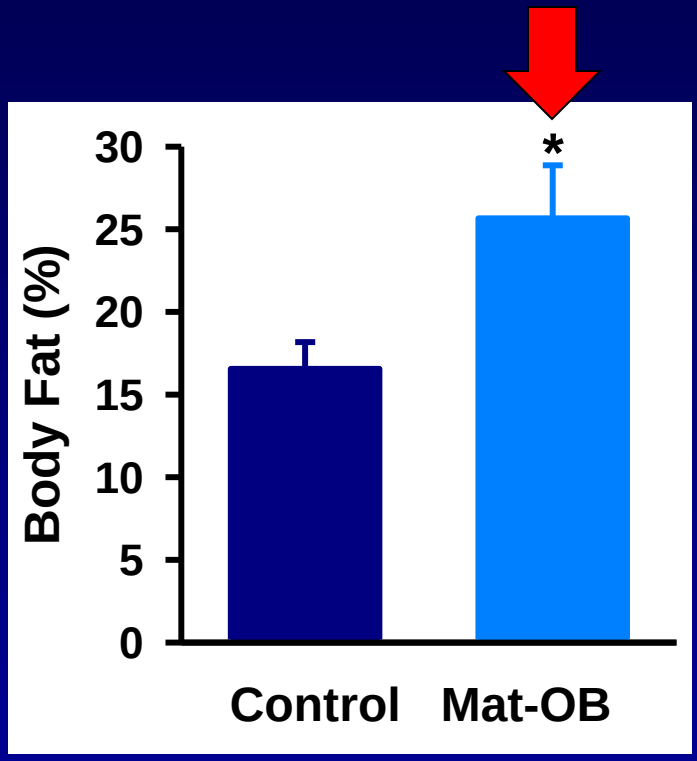
Mean ± SE; * p < 0.01

Percentage Body Fat: Male Offspring

3 Weeks



6 Months

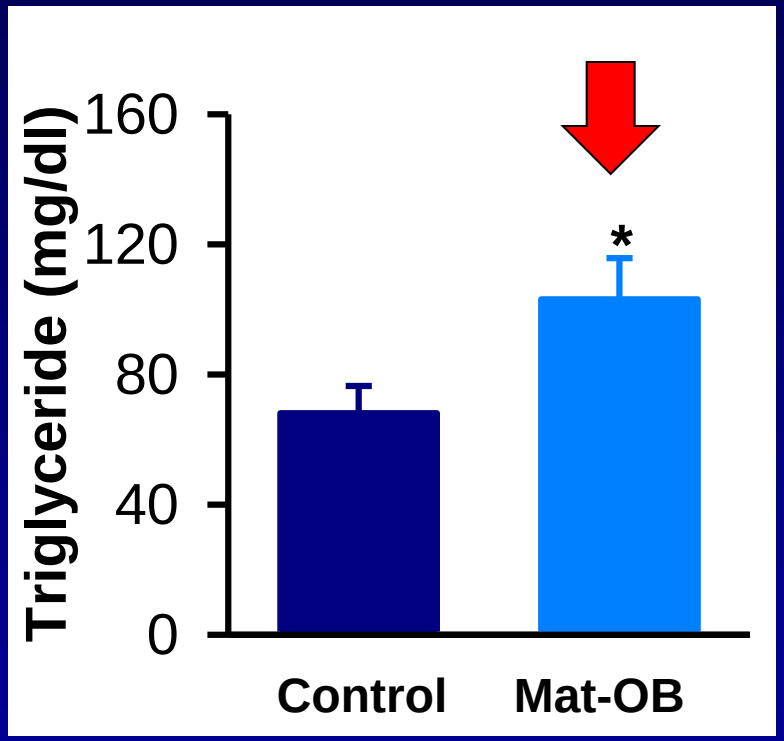


Early Onset Obesity

Mean ± SE; * p < 0.001

Plasma Triglycerides: Male Offspring

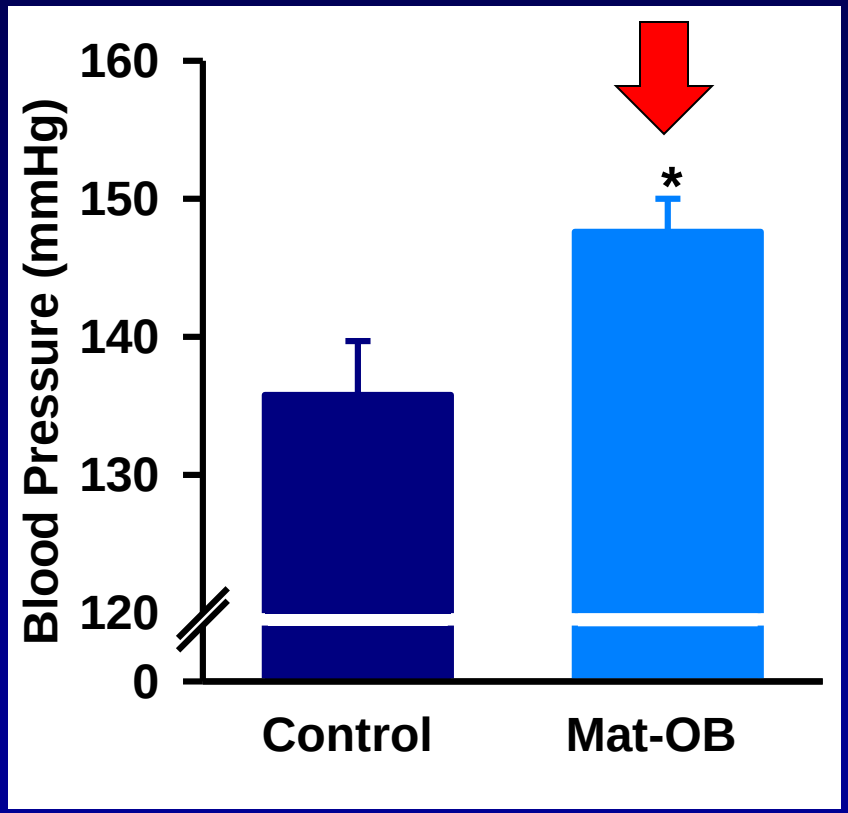
3 Weeks



Hypertriglyceridemia

Mean ± SE; * p < 0.01

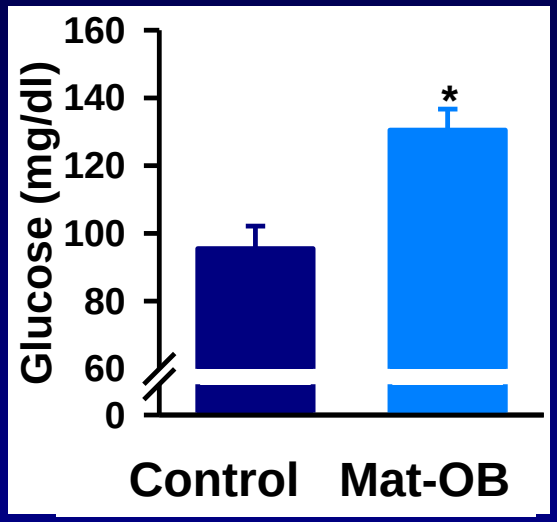
Systolic Blood Pressure
6 Week Obese Males

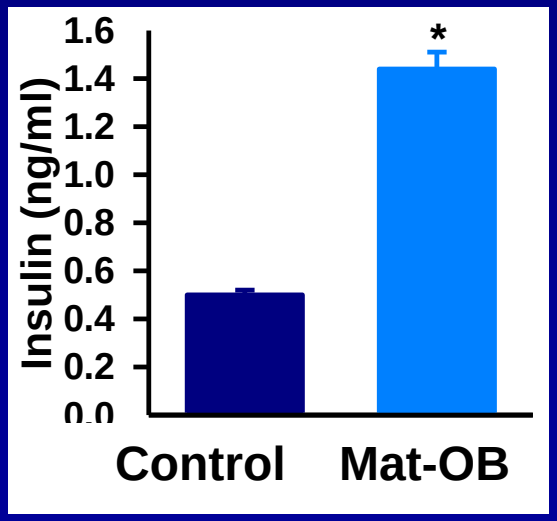


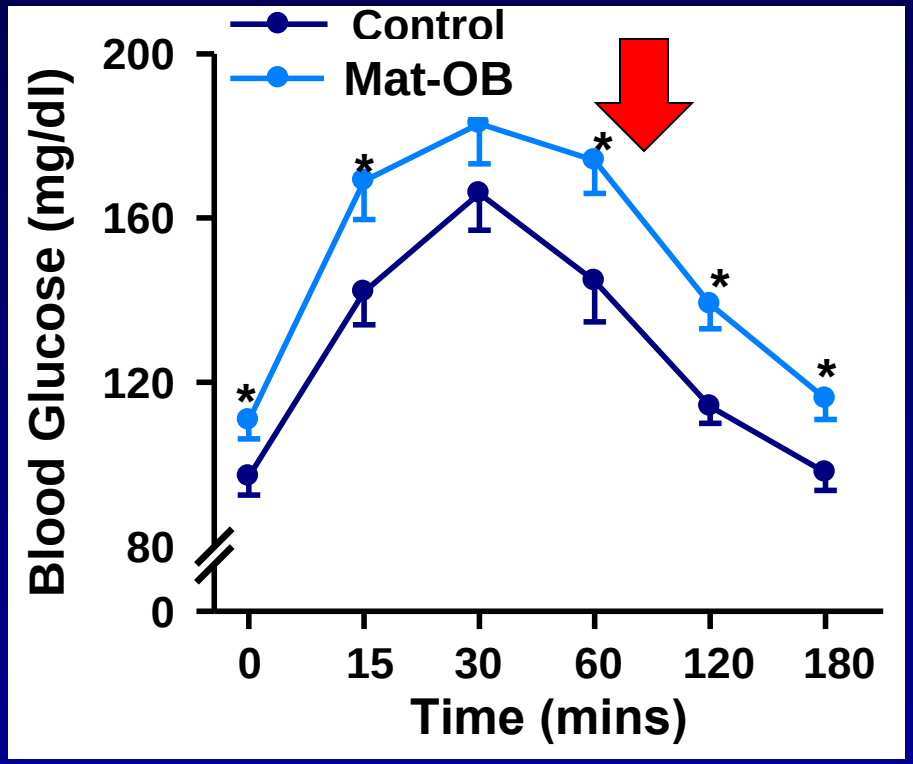
Early Onset Hypertension

*** P < 0.05 vs. Control**

Diabetes: Insulin Resistance
3 Month Obese Males







Insulin Resistance

Maternal Undernutrition and Overnutrition: Offspring Programming of Metabolic Syndrome

Obesity

Adiposity

Hypertension

Hyperlipidemia

Fatty Liver

Diabetes

Programming Mechanisms

Lung

Pulmonary Insufficiency

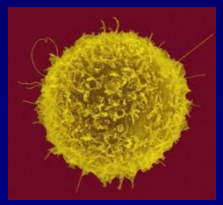
Appetite → Increased Food Intake

Placenta

Placental Dysfunction

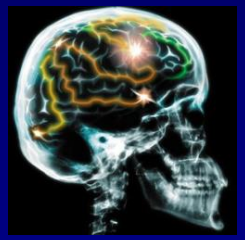
IMPAIRED MATERNAL NUTRITION

Immune



Immune Deficiency

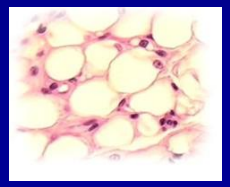
Brain



Neurogeneration

Blood vessels

Hypertension

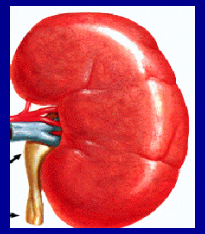


Altered adipose

Obesity

Defective β cell function

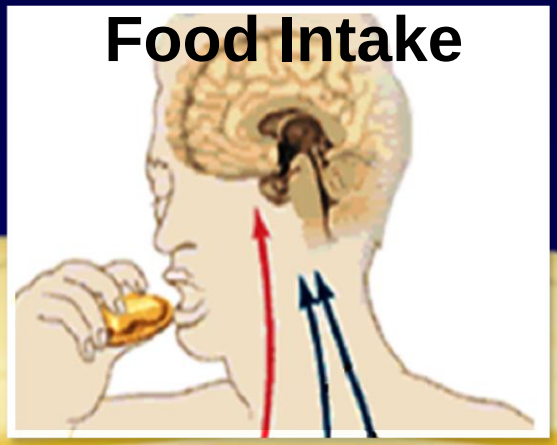
Insulin deficiency



Renal

Renal Insufficiency

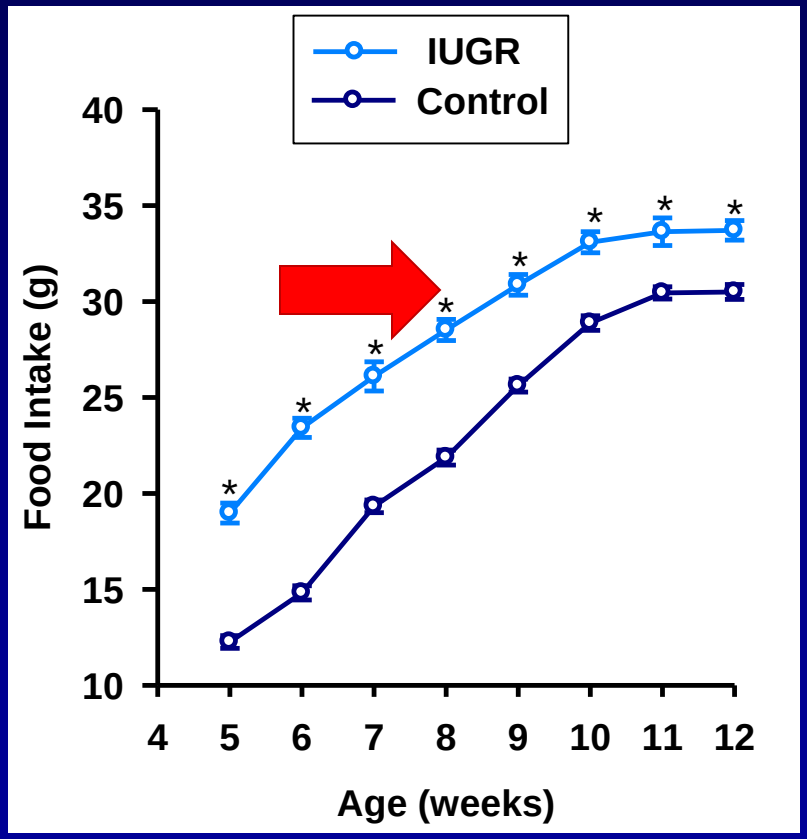
Major Contributors of Obesity



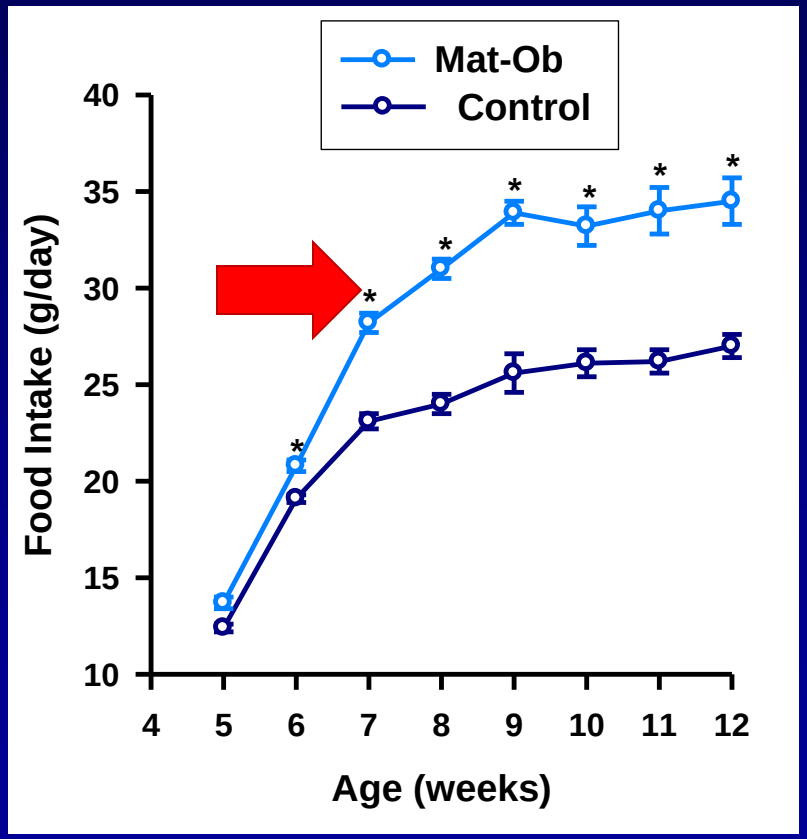
“Appetite Efficiency”
Time Spent Eating vs. Obesity Rate

Mechanism of Obesity
Increased Food Intake

Under-Nutrition

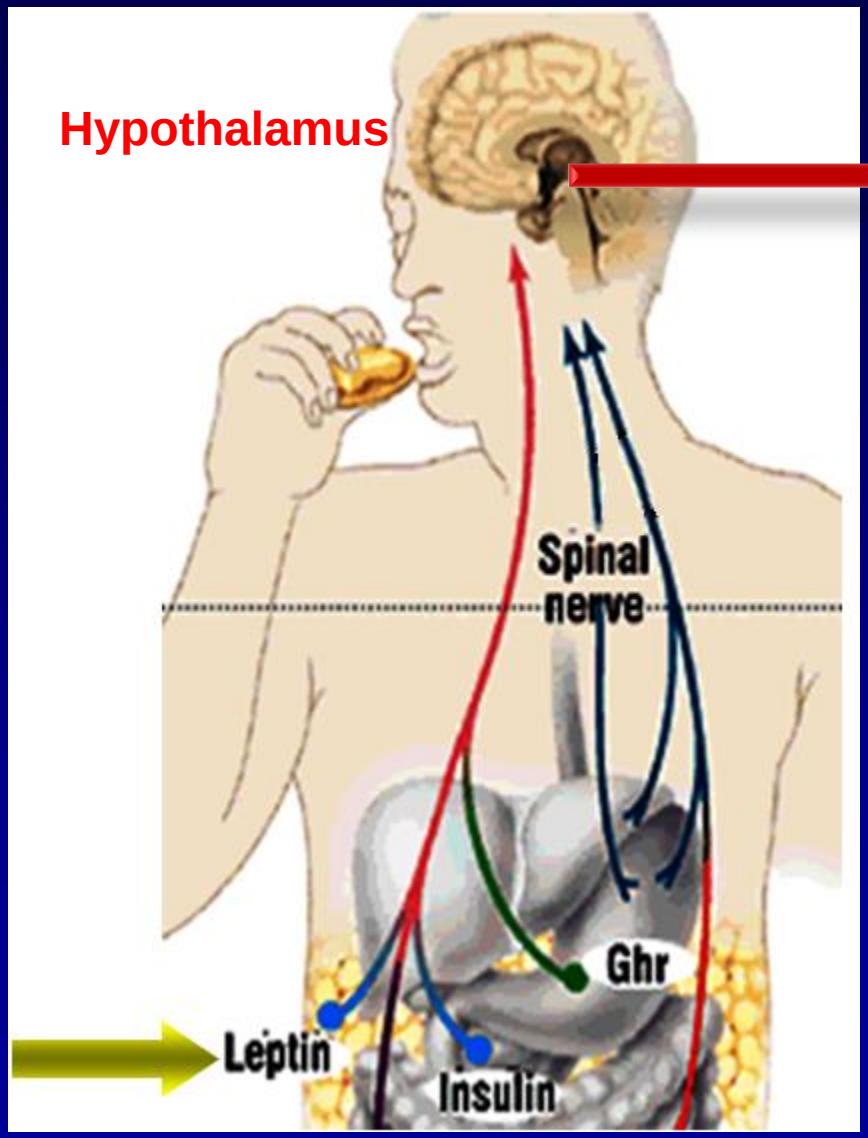


Over-Nutrition



Weekly food intake; Mean ± SE

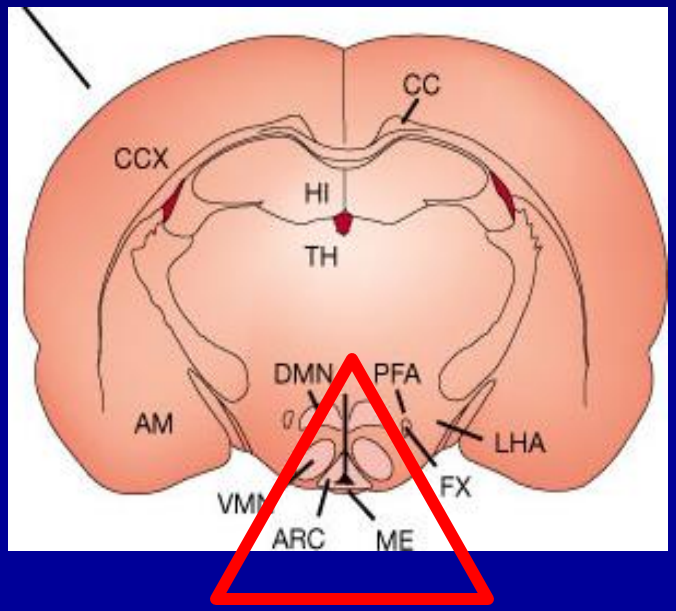
Appetite Regulation

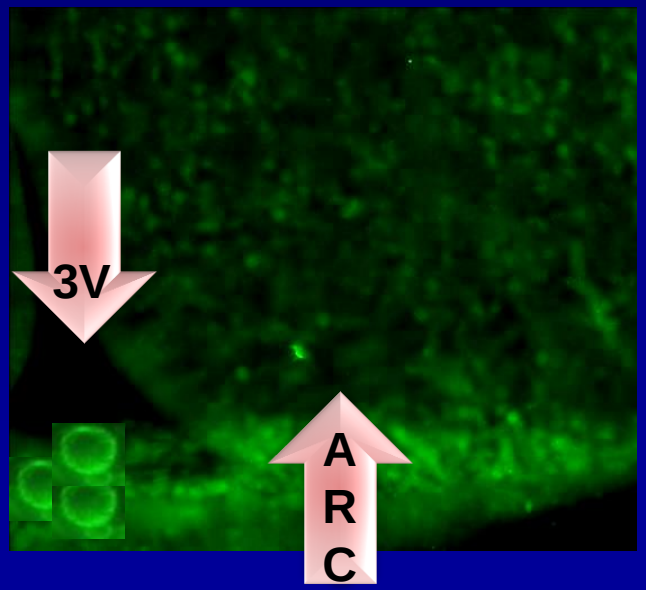


ARC Nucleus Development

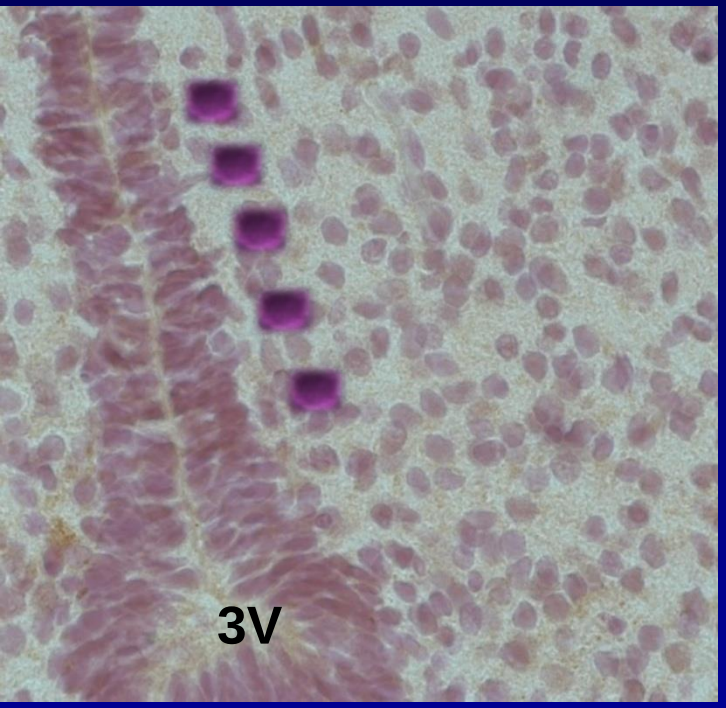
- ARC cells arise from Neural Stem Cells in periventricular region
- Appetite (NPY) and Satiety (POMC) neurons populate the ARC during fetal life and this continues to develop during postnatal life

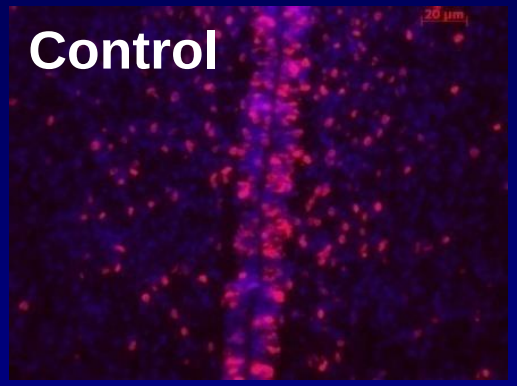
Appetite Regions

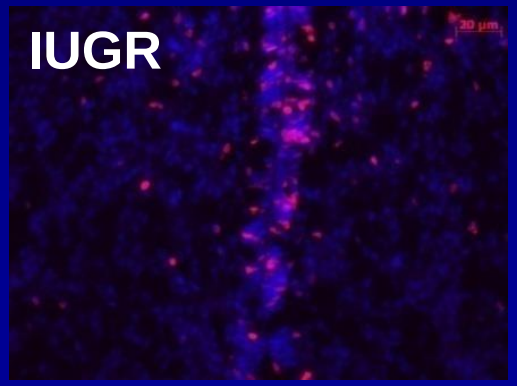


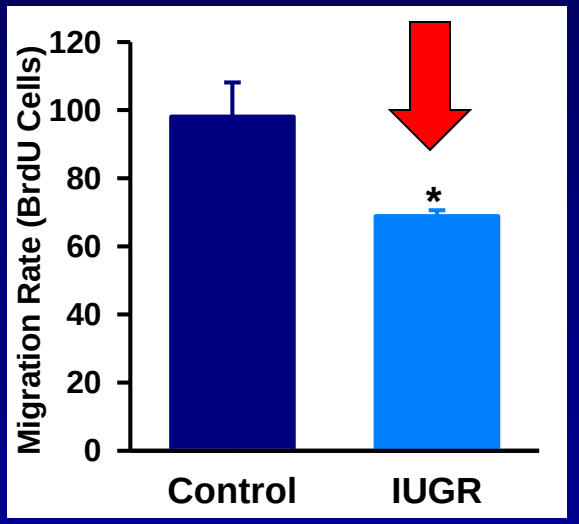


In Vivo Neural Stem Cell Migration
1 Day Newborn Hypothalamus









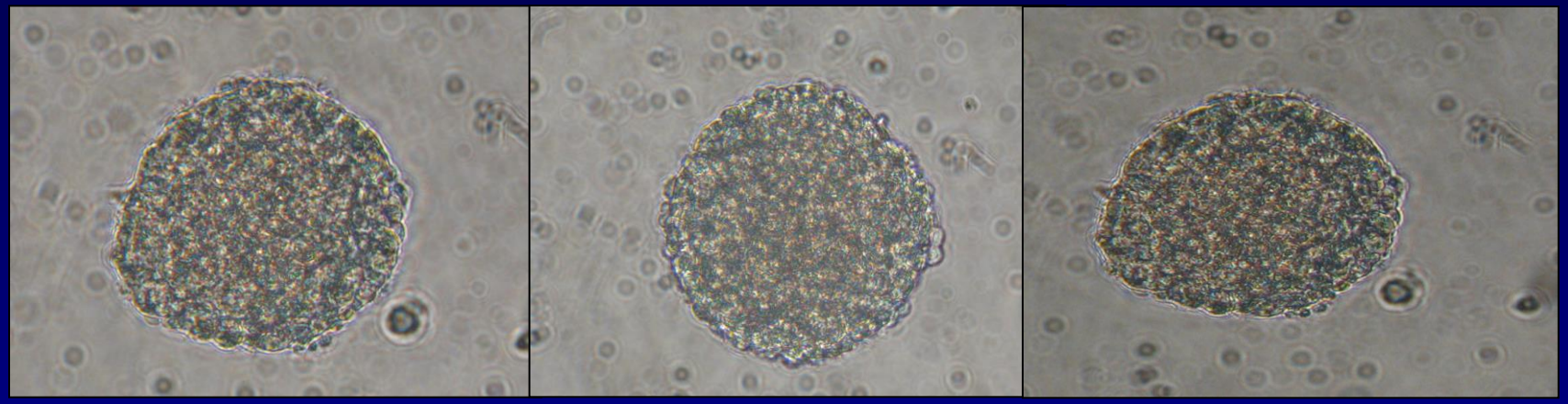
* P < 0.01

3V = Third Ventricle

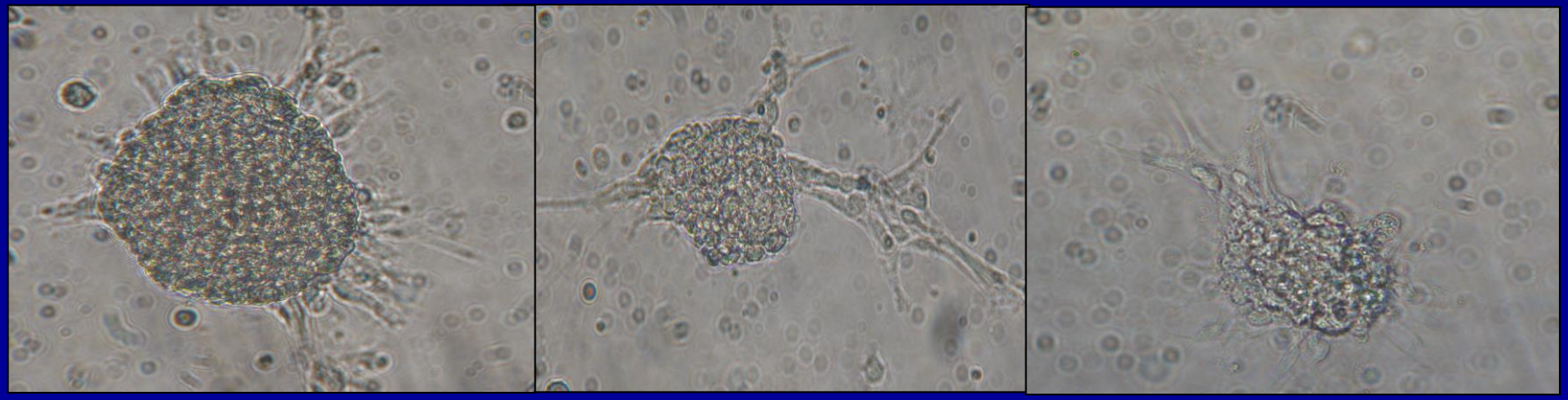
Nestin = marker of NSC
BrdU = proliferation

Hypothalamic Neurospheres

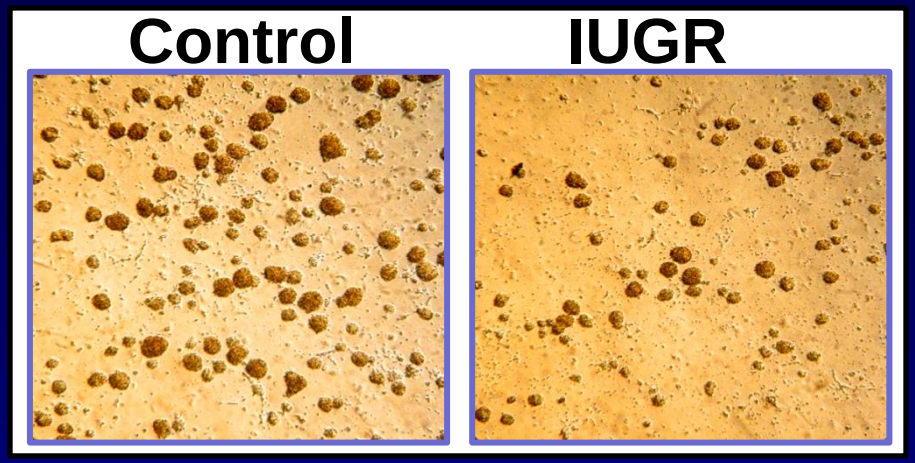
Undifferentiated

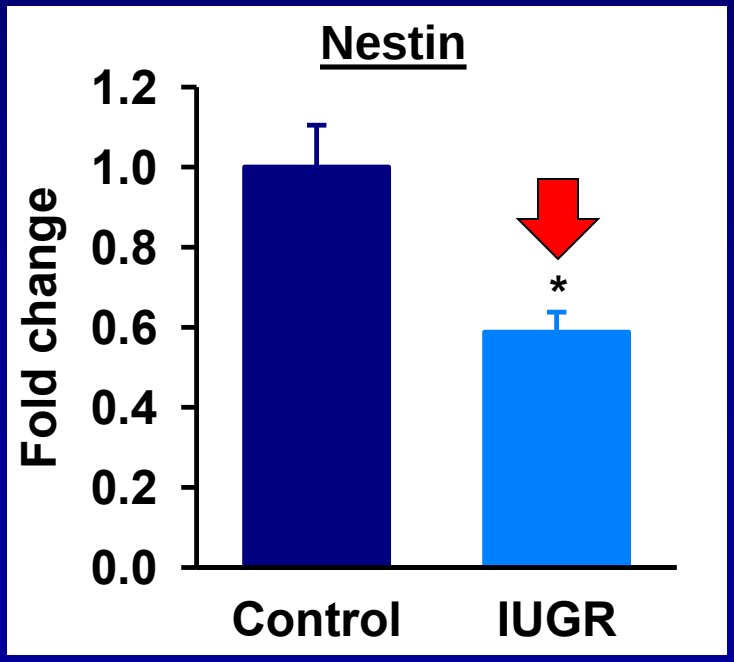


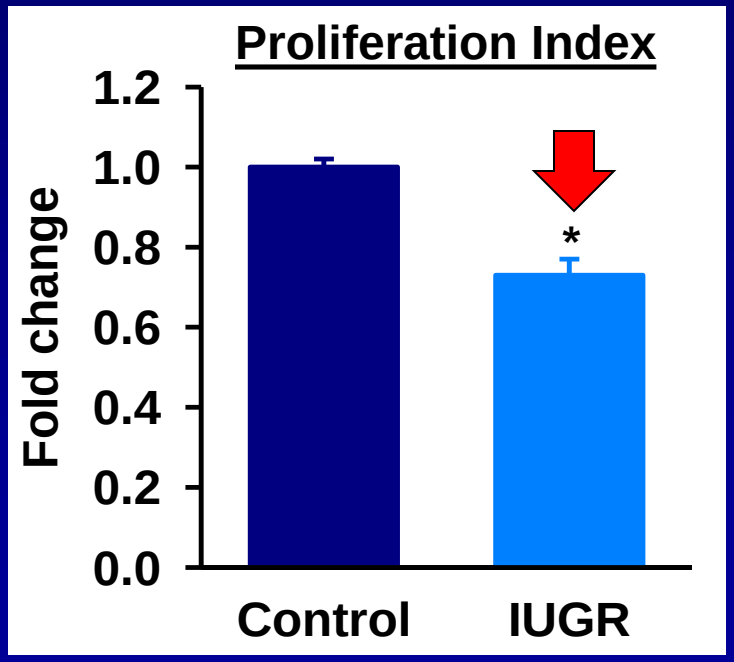
Early Differentiation



Neural Stem Cell Proliferation



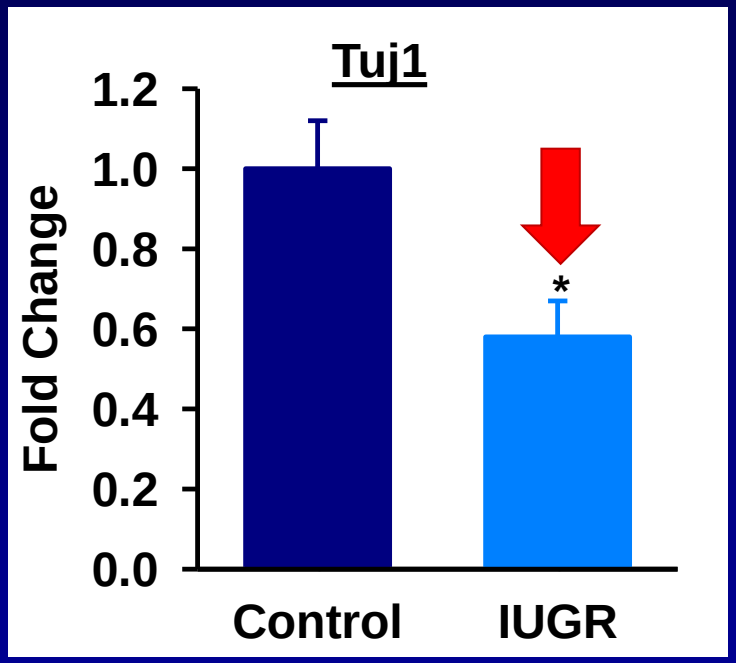




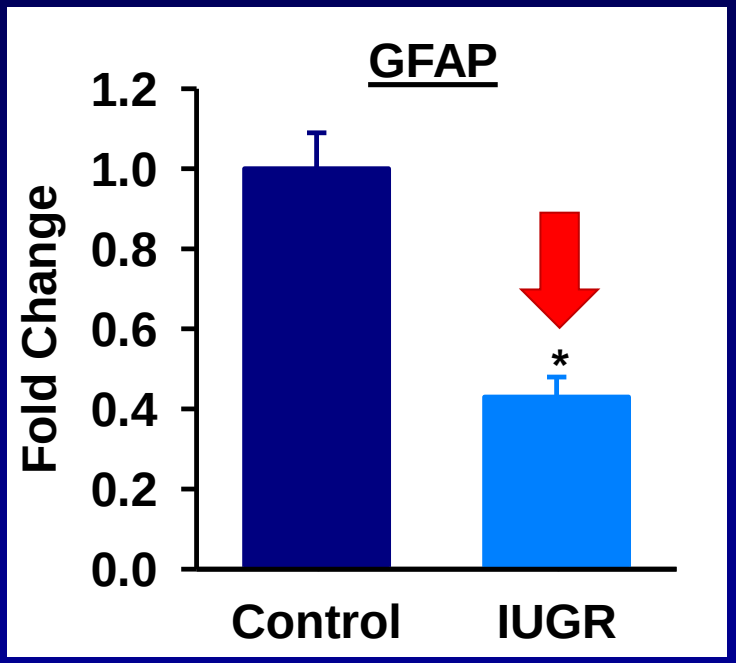
Decreased Proliferation

Neural Stem Cell Differentiation

Neuron

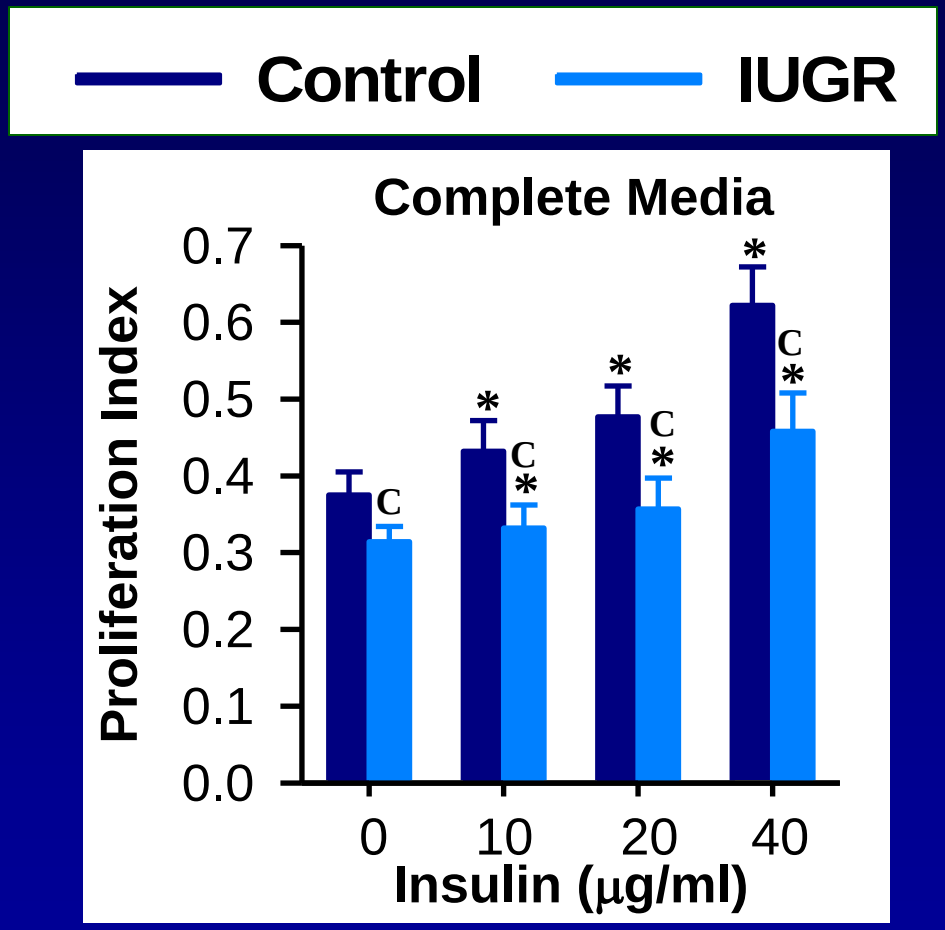


Astrocyte



Decreased Differentiation

Neural Stem Cell Insulin-induced Proliferation



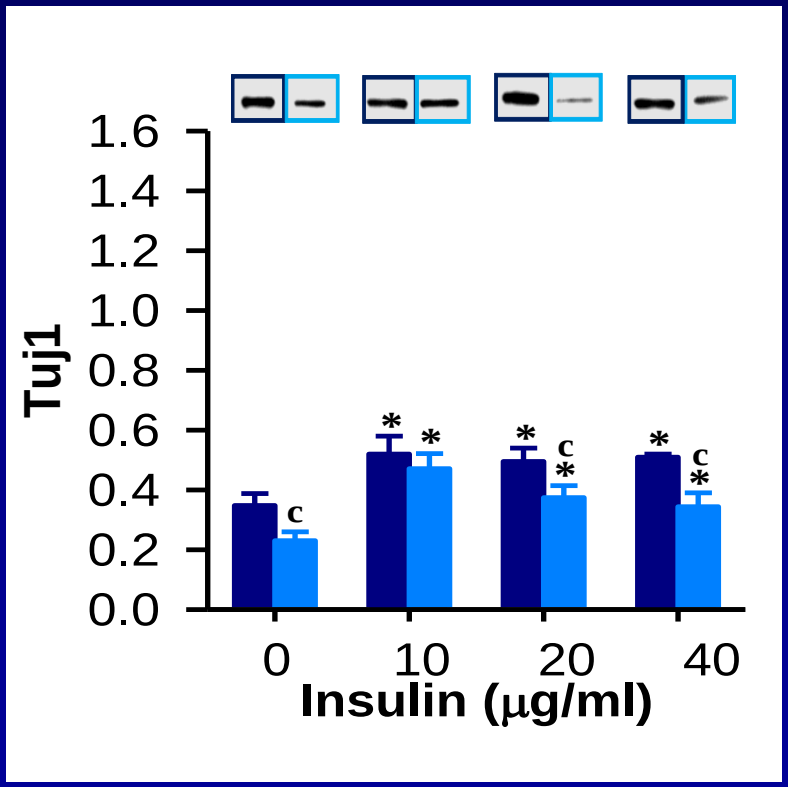
* P < 0.05 vs. 0 ng/ml; ^{c} P < 0.05 IUGR vs. Control

Desai et al, Brain Res, 2011

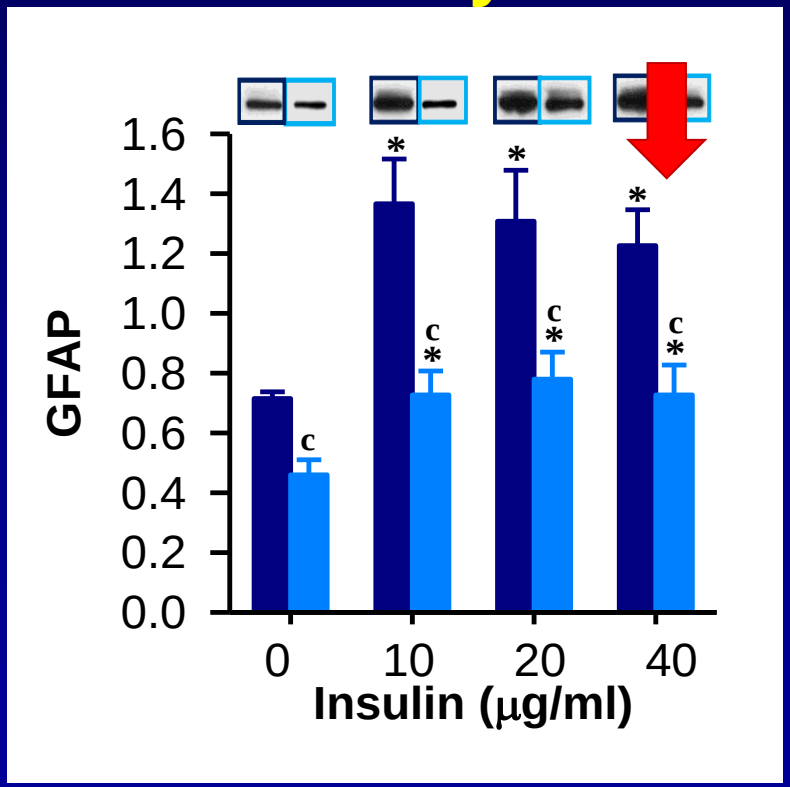
Neural Stem Cell Insulin-induced Differentiation

Control IUGR

Neuron



Astrocyte*

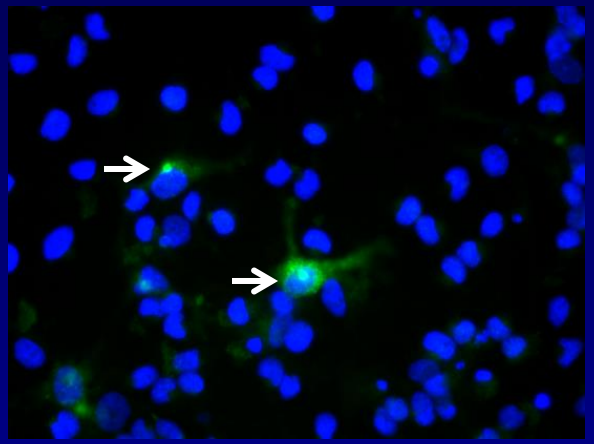


* P < 0.05 vs. 0 μg/ml insulin; ^{c} P < 0.05 IUGR vs. Control

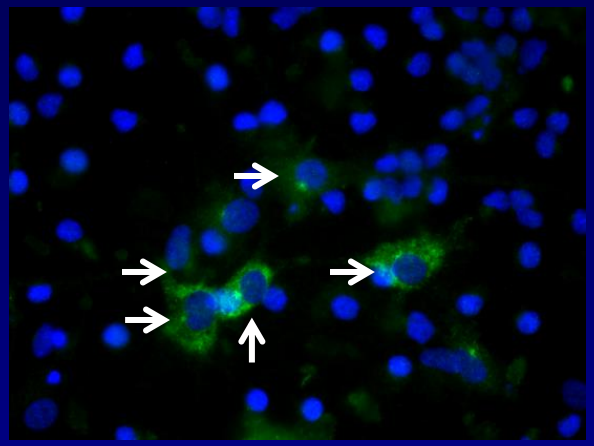
Desai et al, Brain Res, 2011

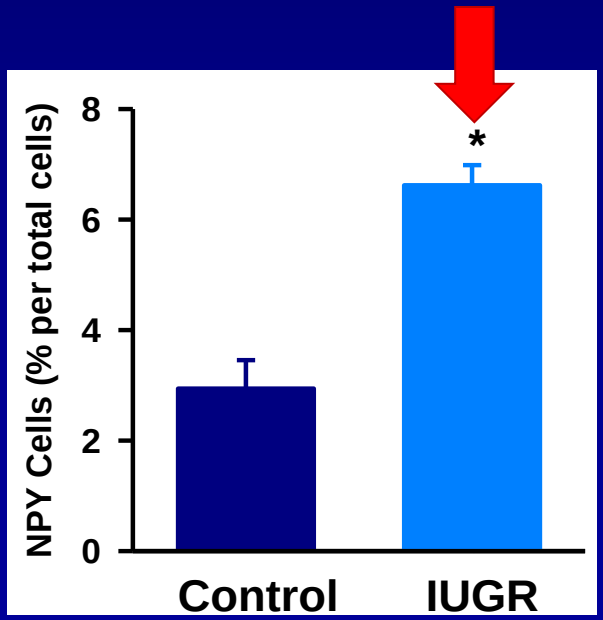
Differentiated Neural Stem Cell Appetite (NPY) Neurons

Control



IUGR



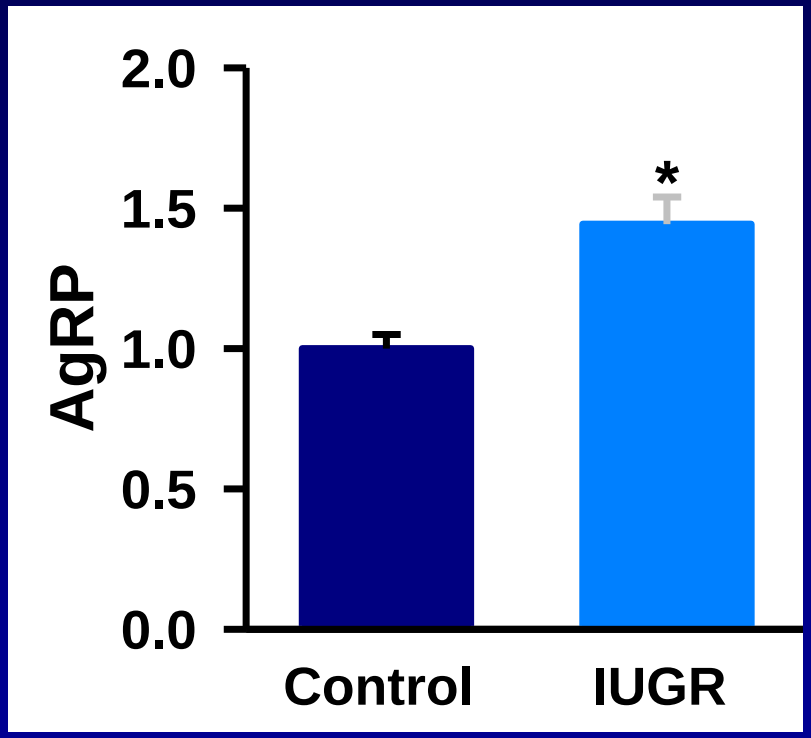


Increased NPY
(appetite neurons)

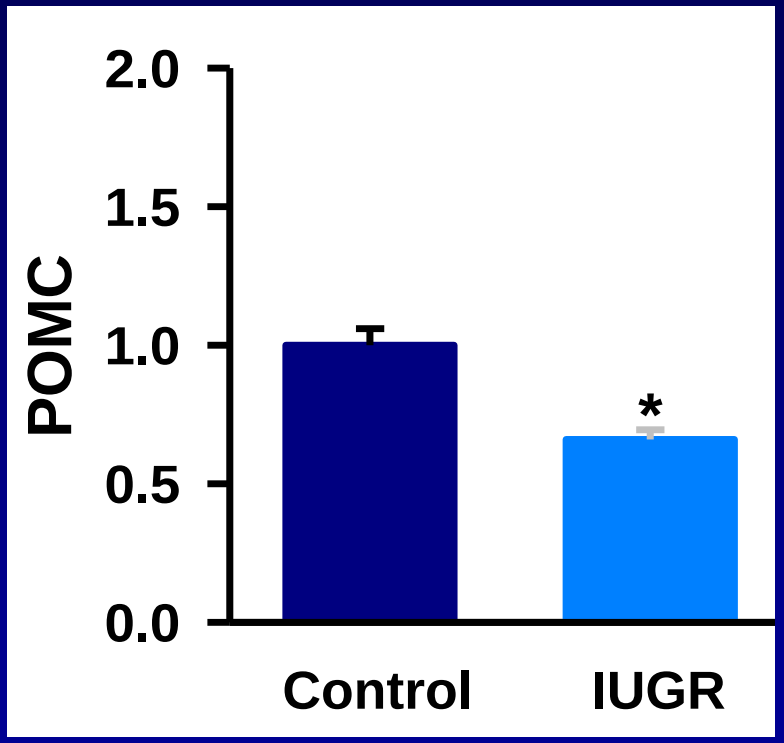
* P < 0.05 vs. Control

Hypothalamic Tissue Protein: 1 Day FR

↑ Appetite



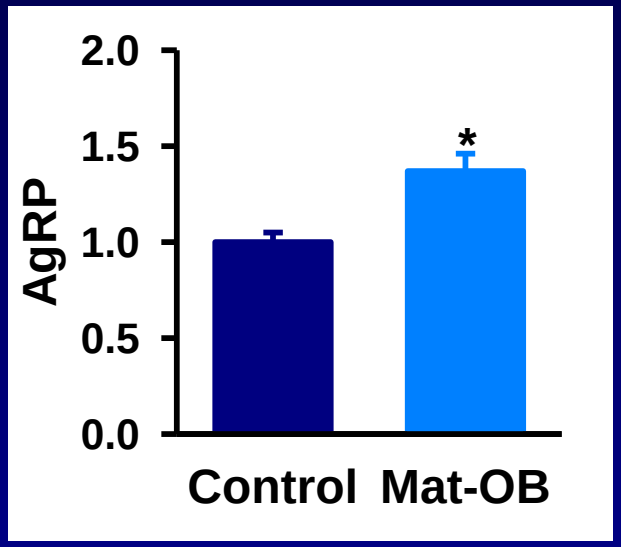
↓ Satiety



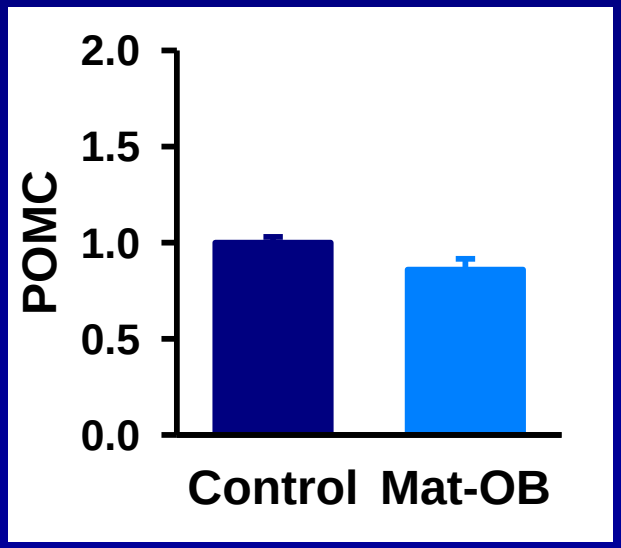
Increased Appetite to Satiety Ratio

Mat-OB: Hypothalamic Tissue Protein

1 Day Old

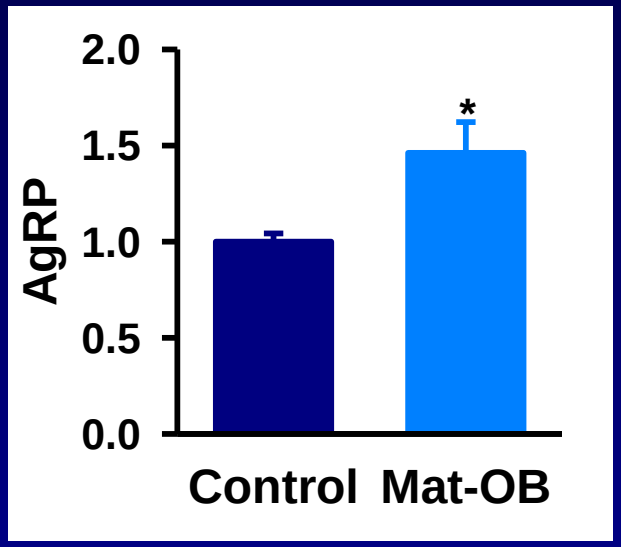


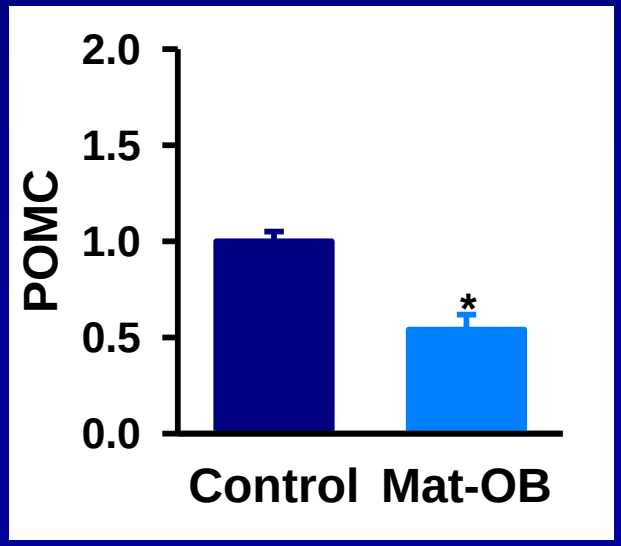
Appetite



Satiety

6 Month Adult

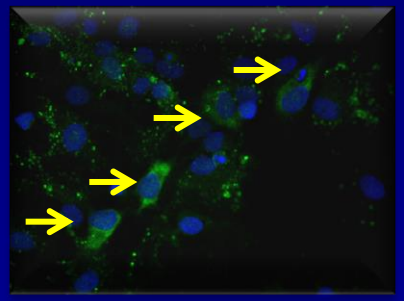




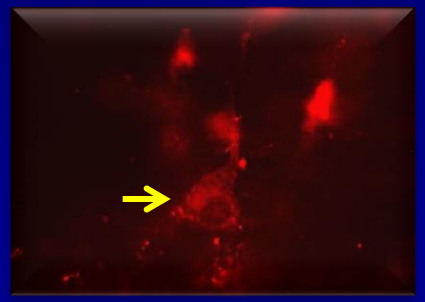
Mechanism of Enhanced Appetite

Altered Nutrition

Appetite (NPY) neurons

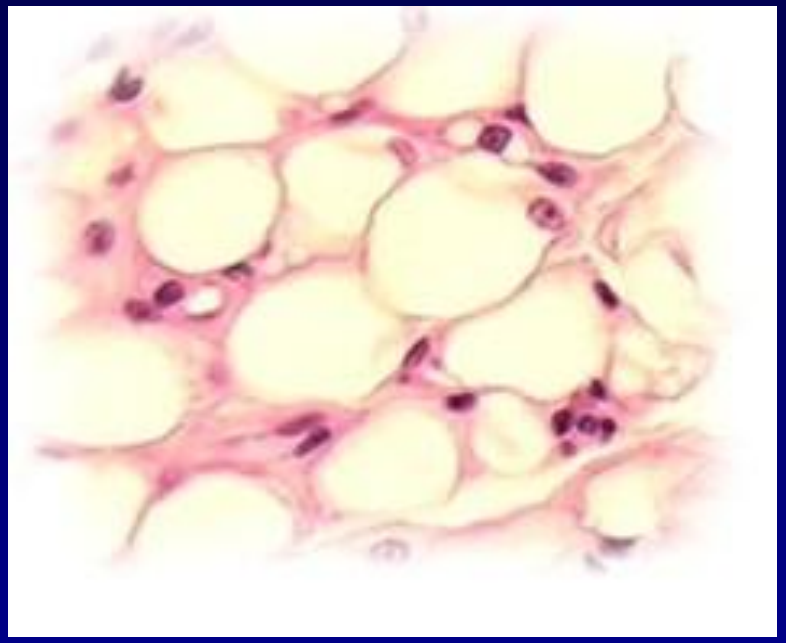


Satiety (POMC) neurons



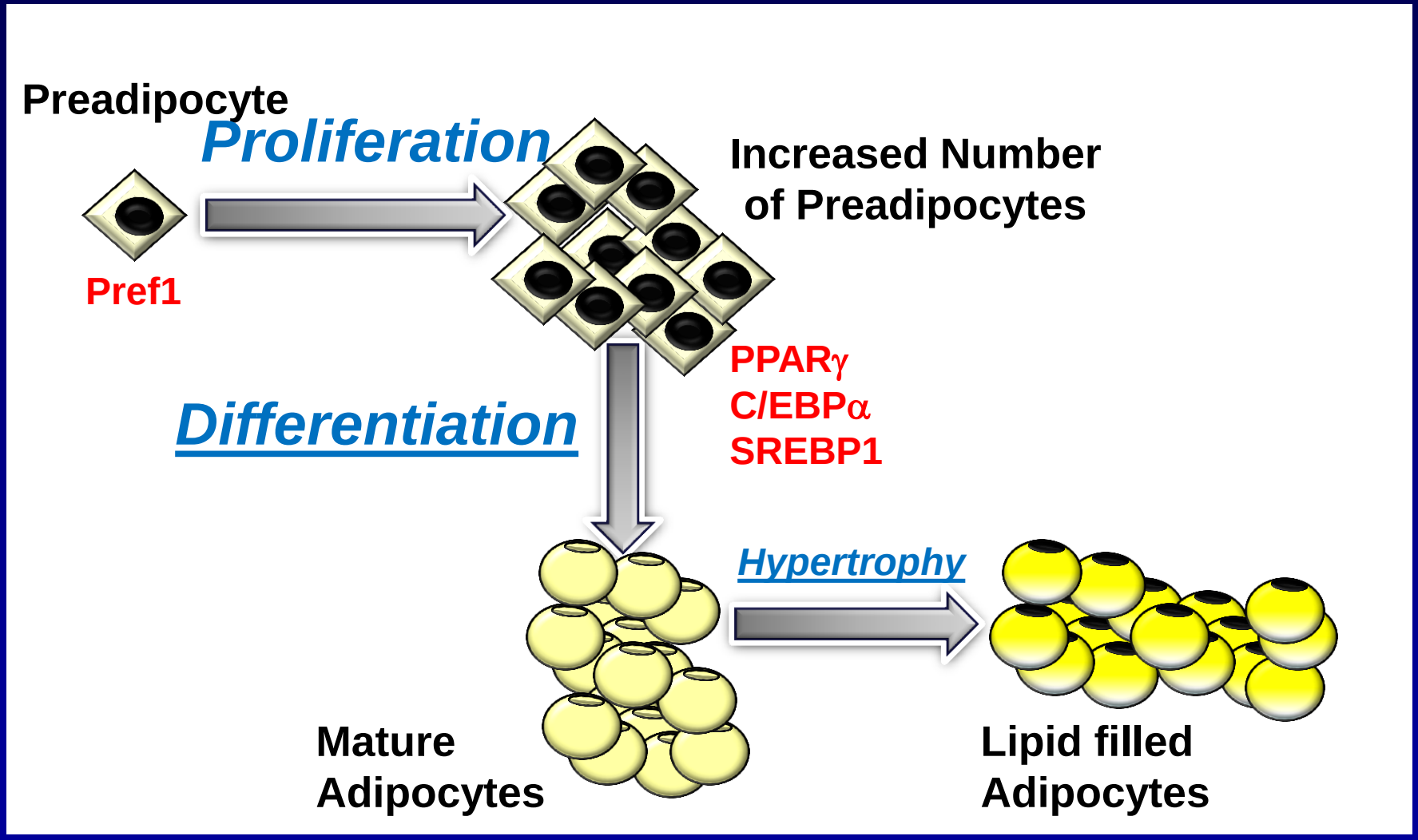
Increased Food Intake

What Programs Adiposity ?



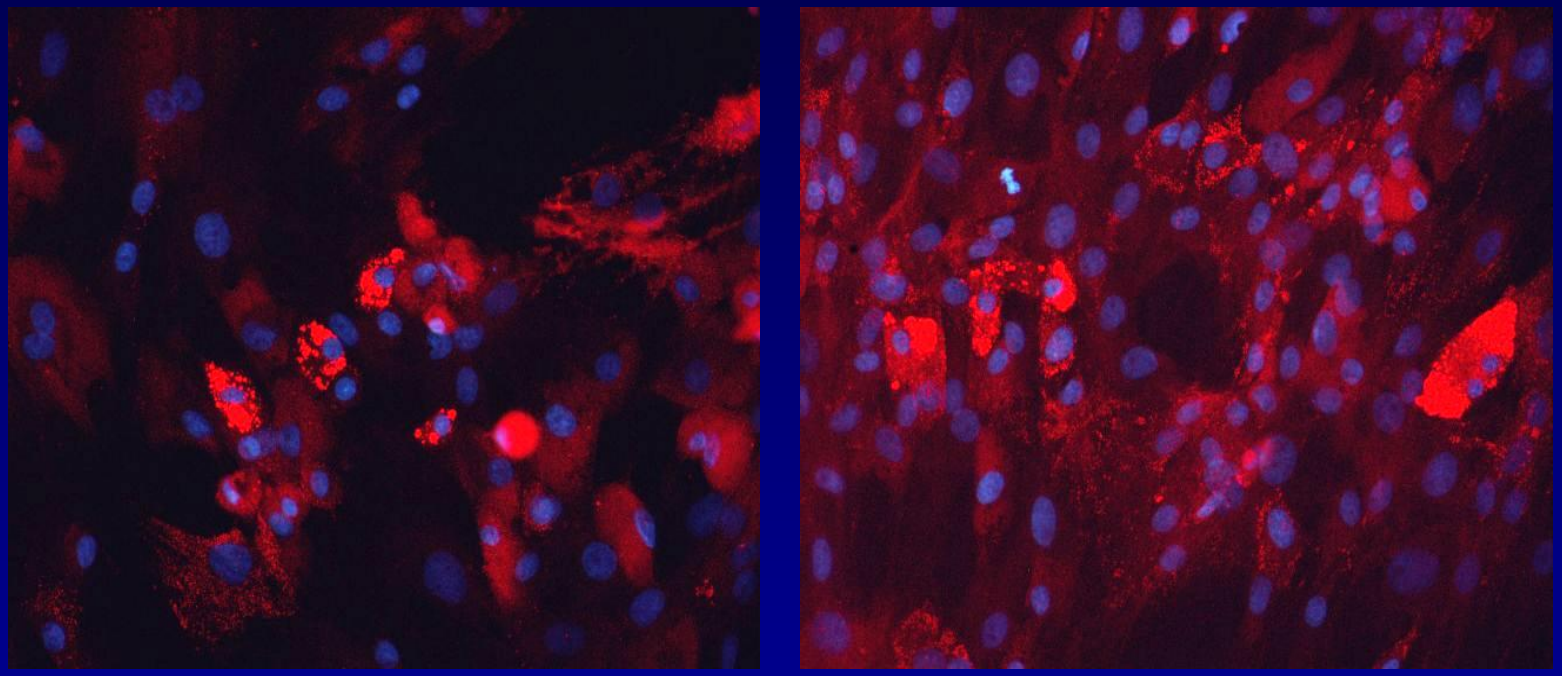
- Adipose Proliferation and Differentiation
- Lipogenesis

Adipogenesis



Primary Cell Culture

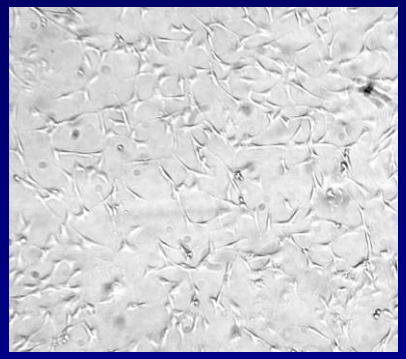
Control **IUGR**



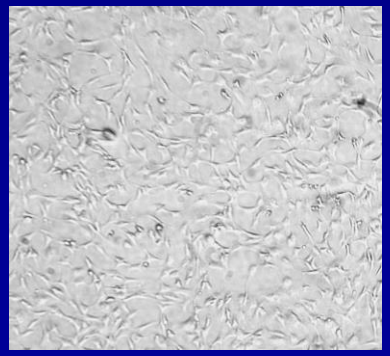
- Adipose tissue from 1 day old offspring
  - Preadipocytes
  - Adipocyte

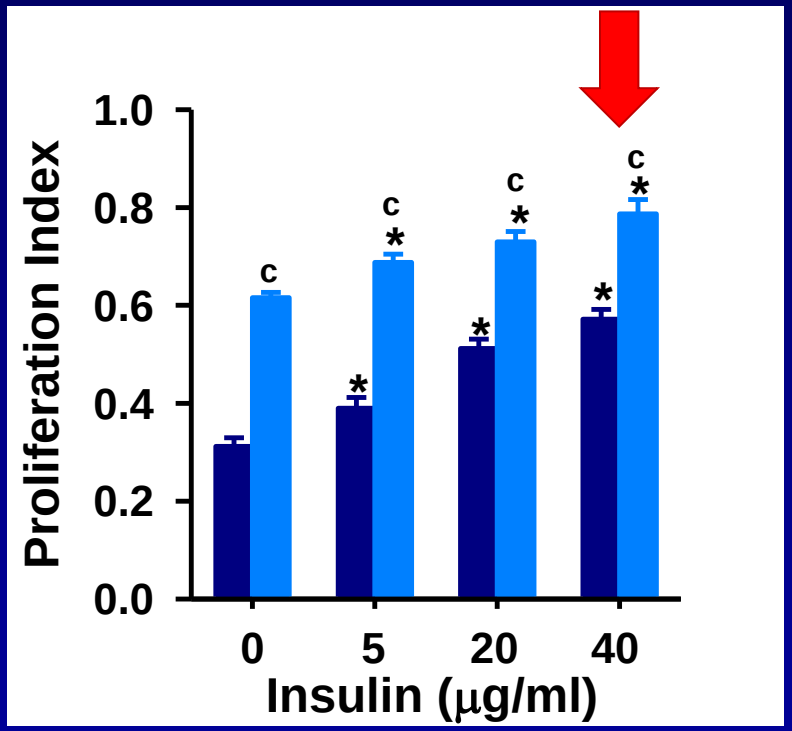
Preadipocytes from 1 Day Newborn
Proliferation

CONTROL



IUGR

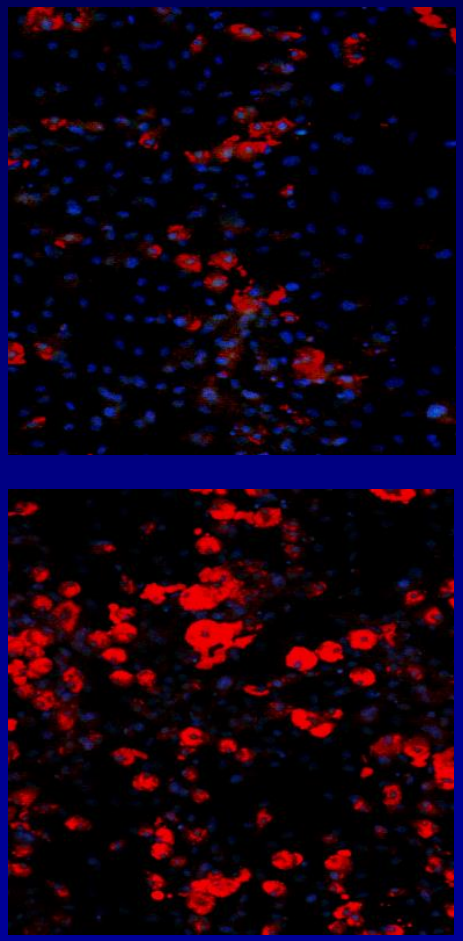


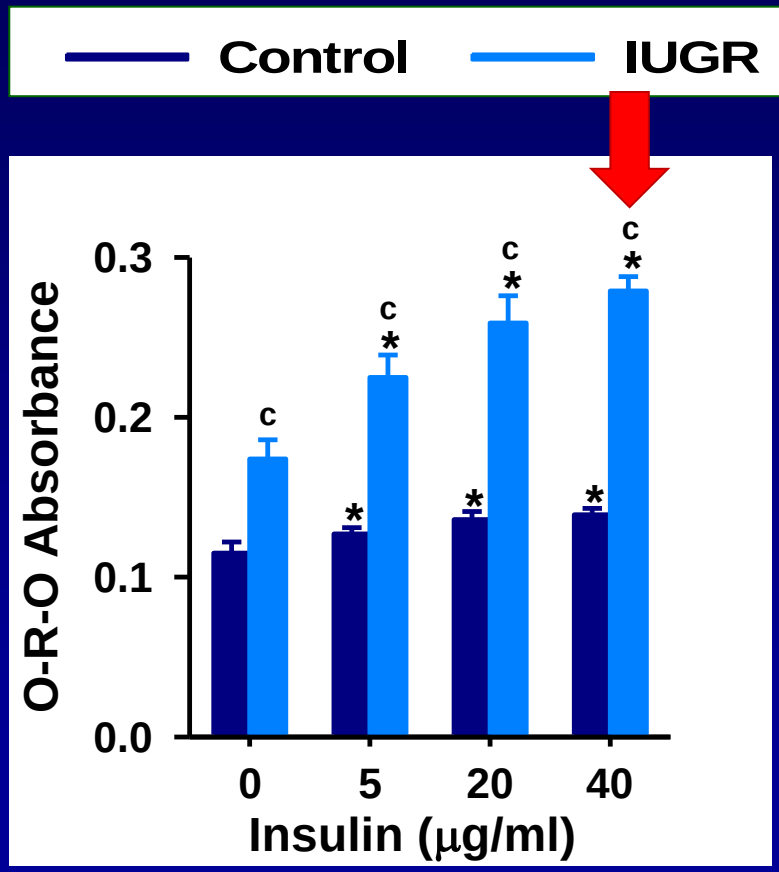


Adipocytes from 1 Day Newborn
Lipid Storage

CONTROL

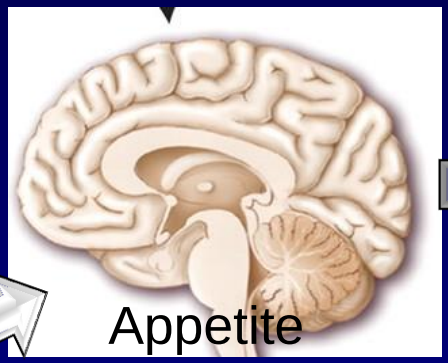
IUGR





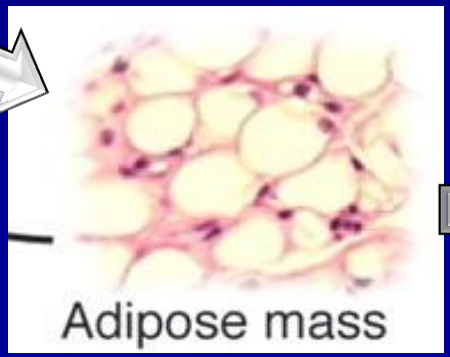
Oil Red Stain; x10

Mechanisms for Developmentally Programmed Obesity/Diabetes

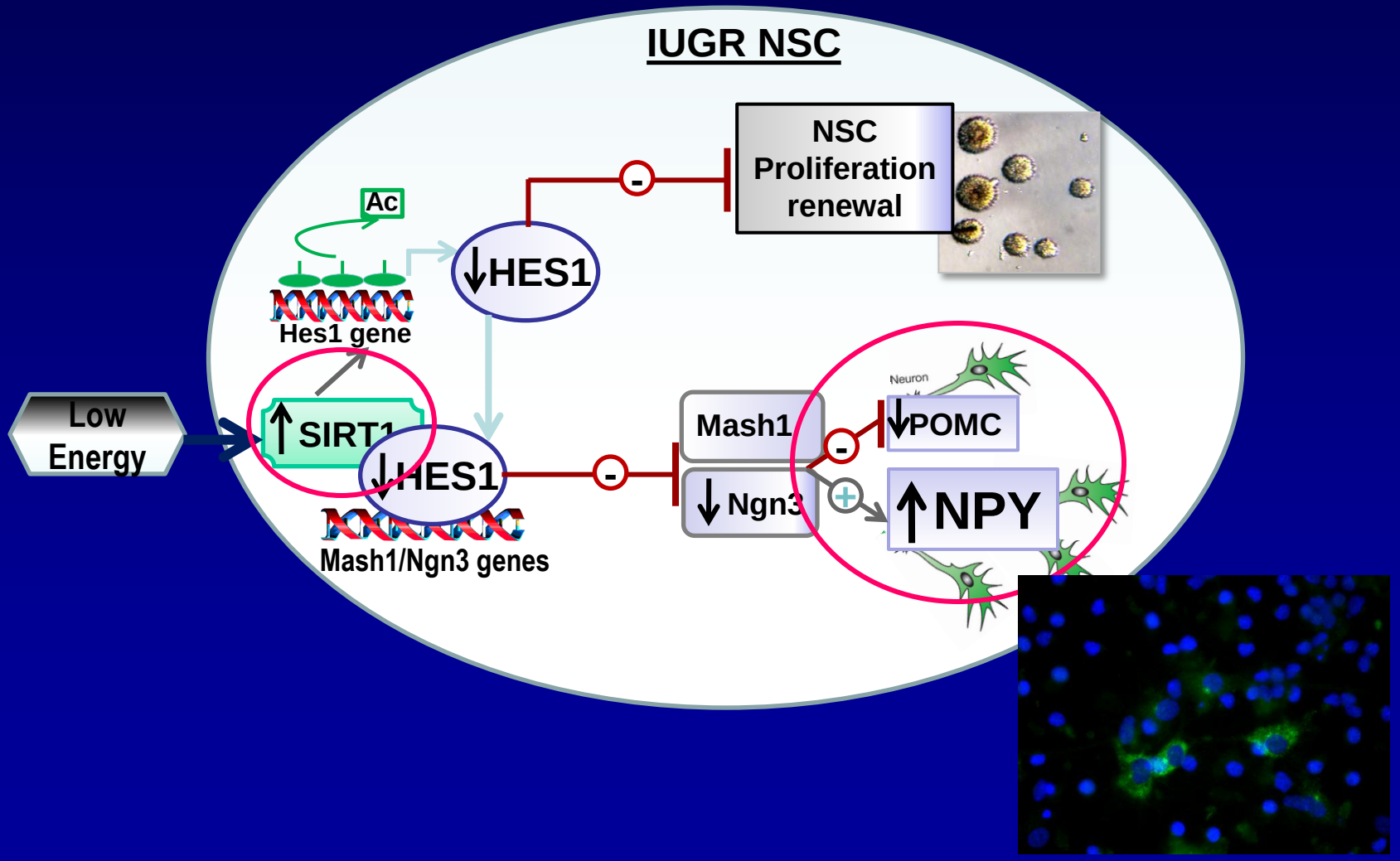


Fetal Nutrition
Maternal
Diabetes

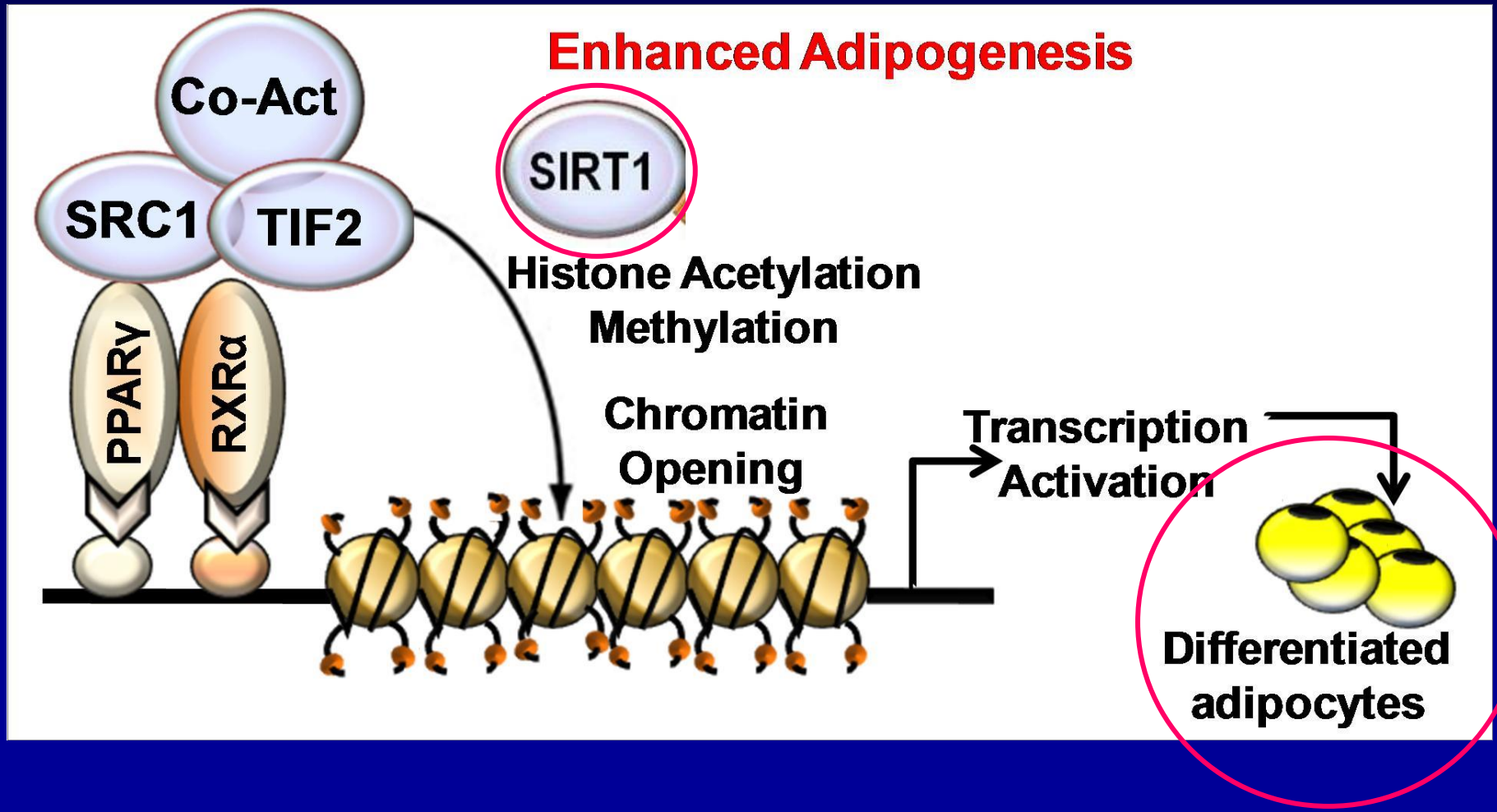
Nutrient Sensors
Cell Signaling
Epigenetic Modifications



Neural Stem Cell Programming:
Nutrient Sensor: Sirt1
Epigenetic Regulation: Histone Deactylase

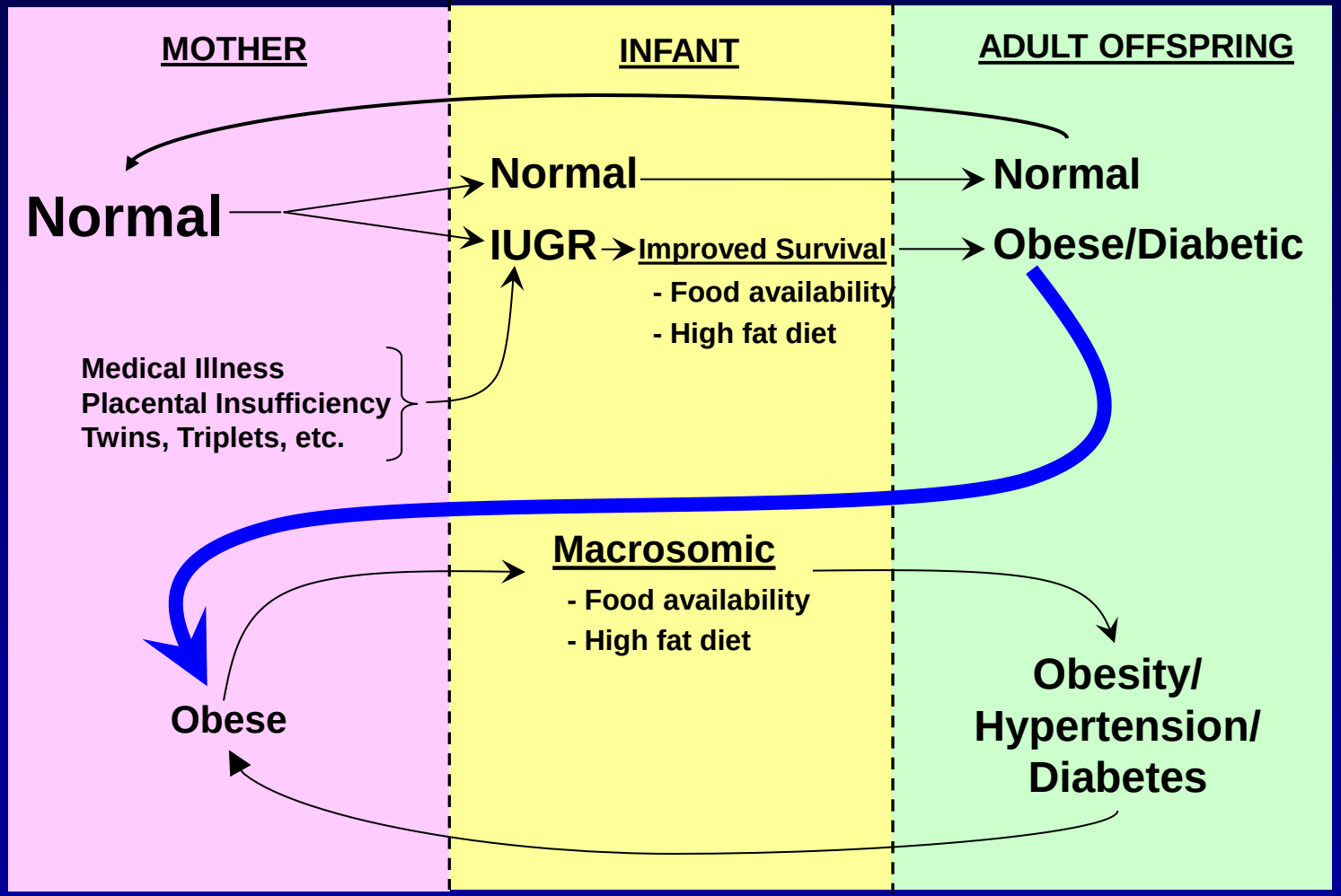


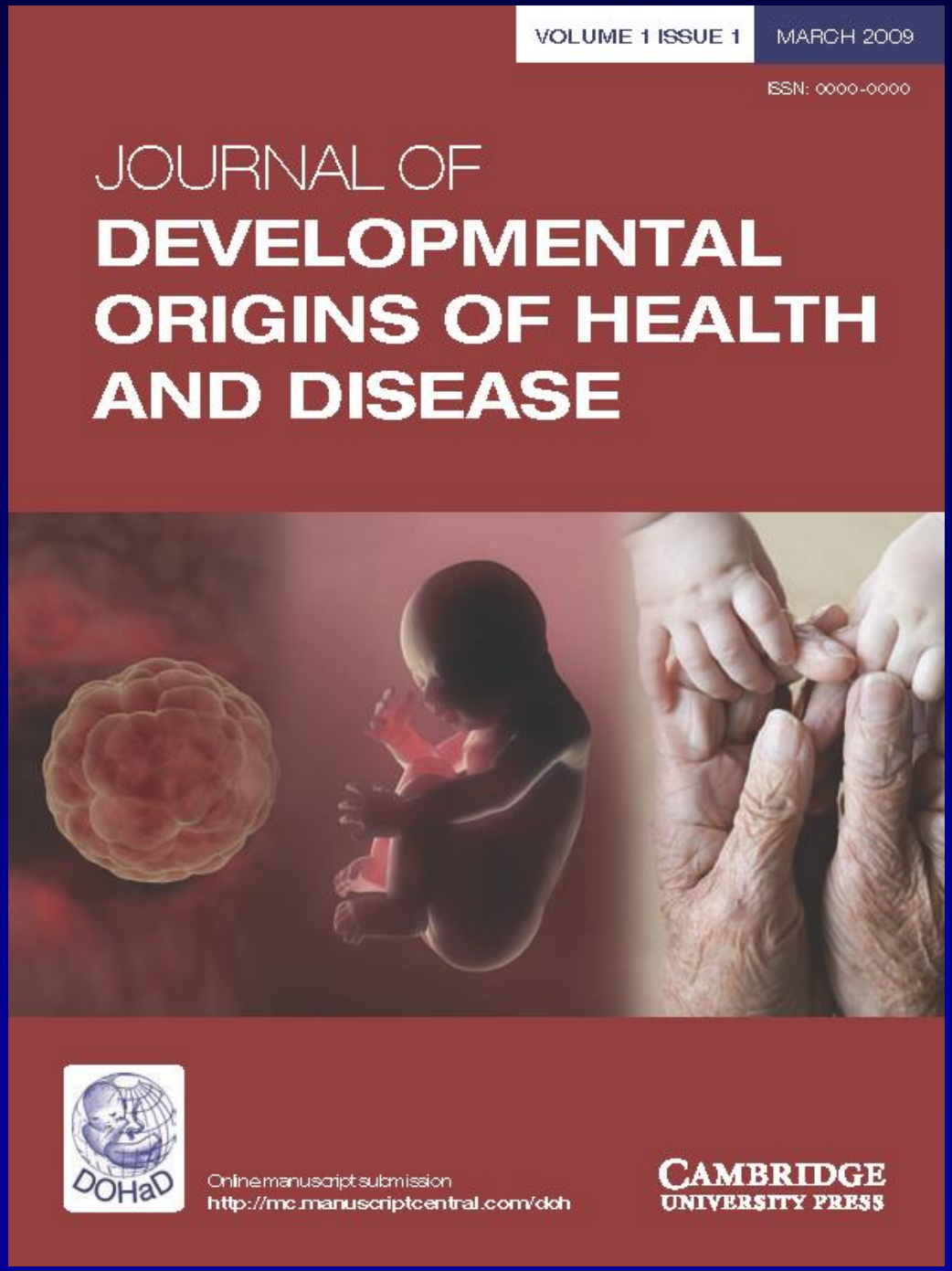
Adipose Stem Cells: Epigenetic Regulation



Equal Appetite/Satiety ?

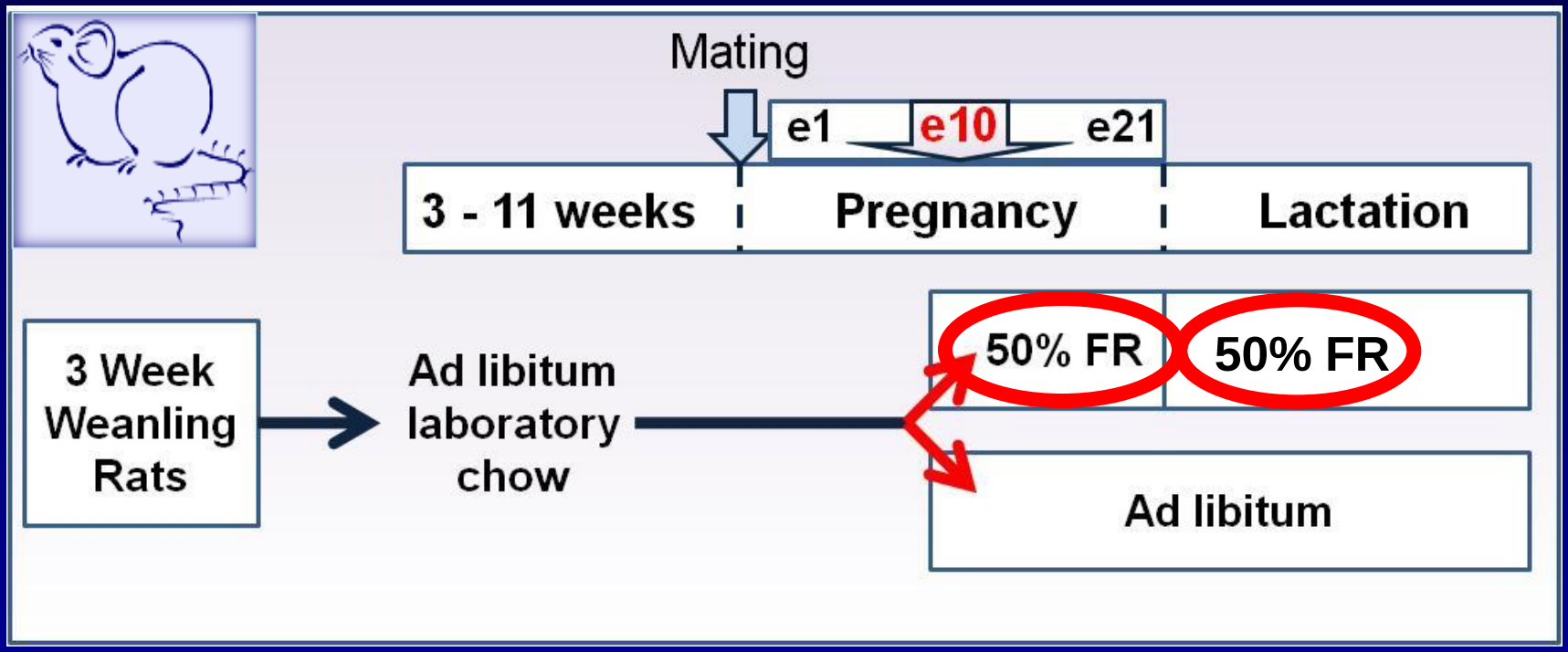
Epidemic of Metabolic Syndrome





Journals.cambridge.org/DOH

Low Birth Weight
Restricted Catch-up Growth

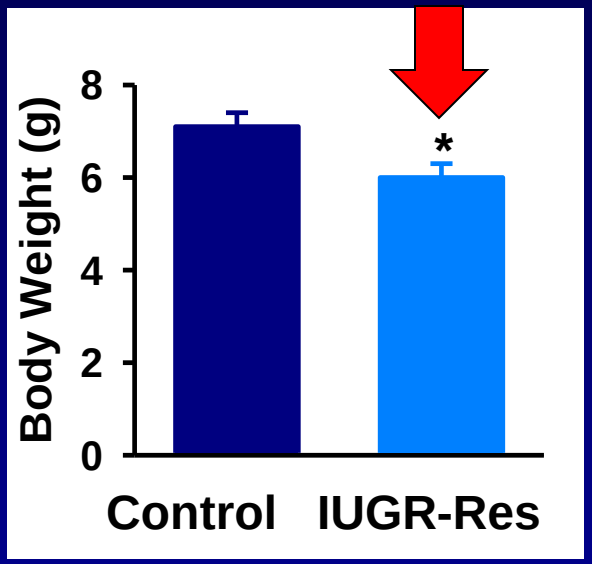


OFFSPRING

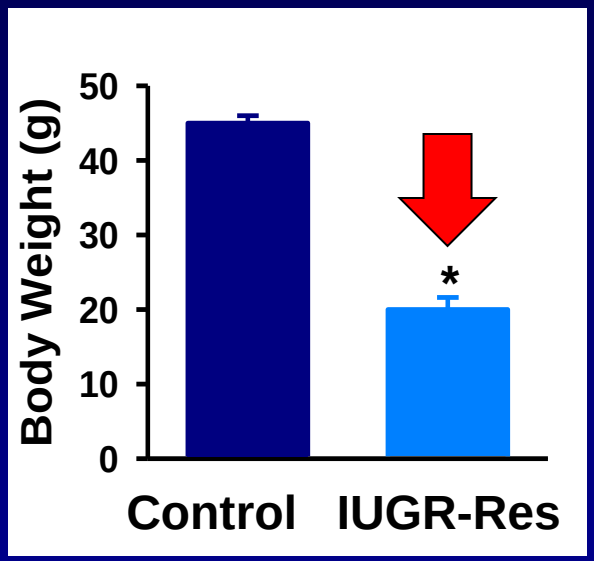
- **Litter size: Culled to 4 males and 4 females at birth**
- **Nursing: All pups cross-fostered to 50% FR fed dams until p21**
- **Weaning: At p21 to ad Libitum food and water**

Body Weight of Male Offspring

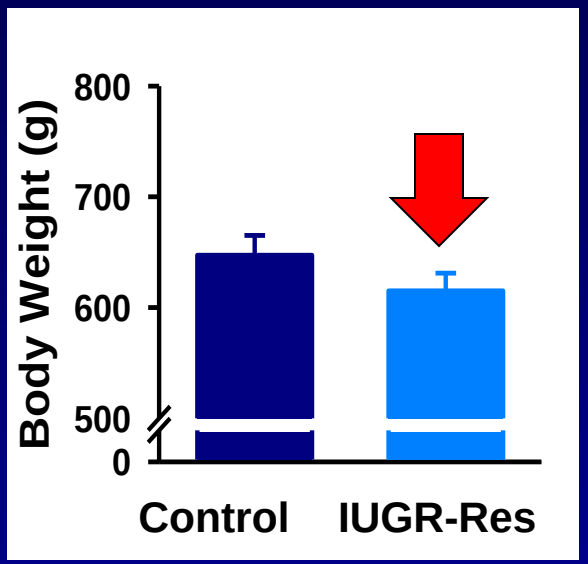
1 Day



3 Weeks



9 Months



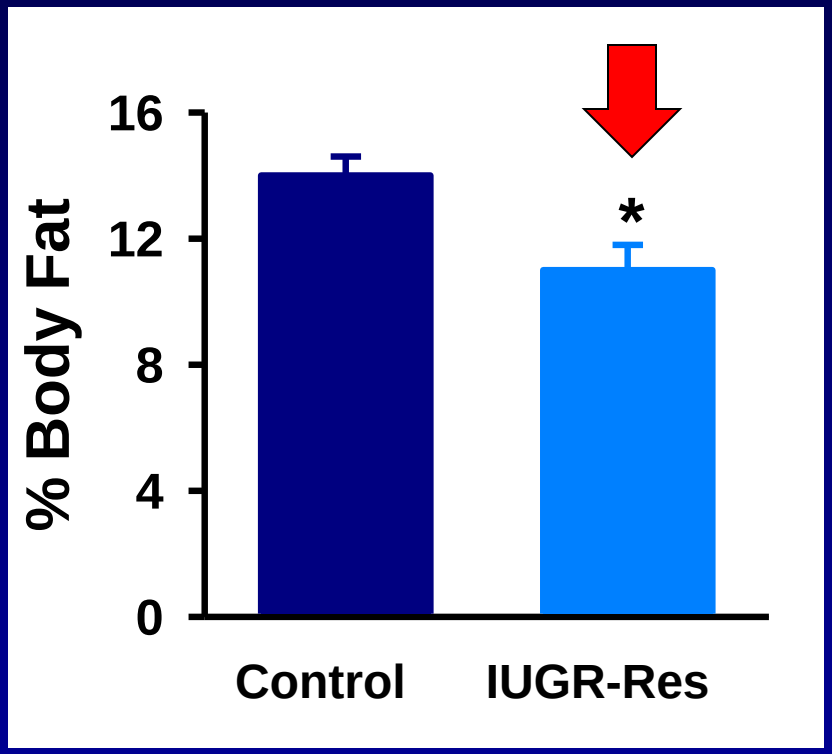
Normal Adult Body Weight

Mean ± SE; * p < 0.01

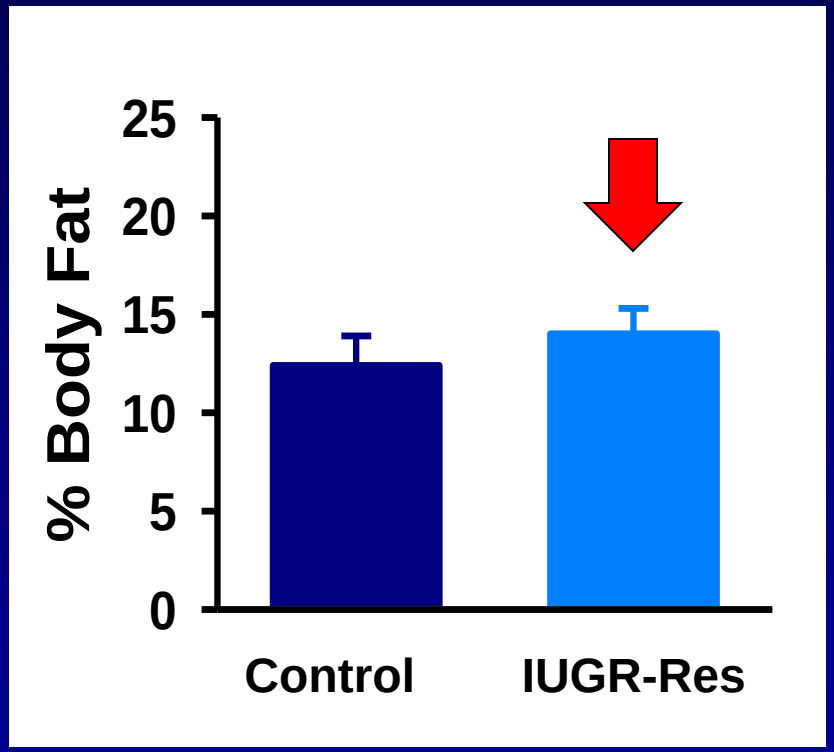
Desai et al, Am J Physiol, 2005

% Body Fat of Male Offspring

3 Weeks



9 Months



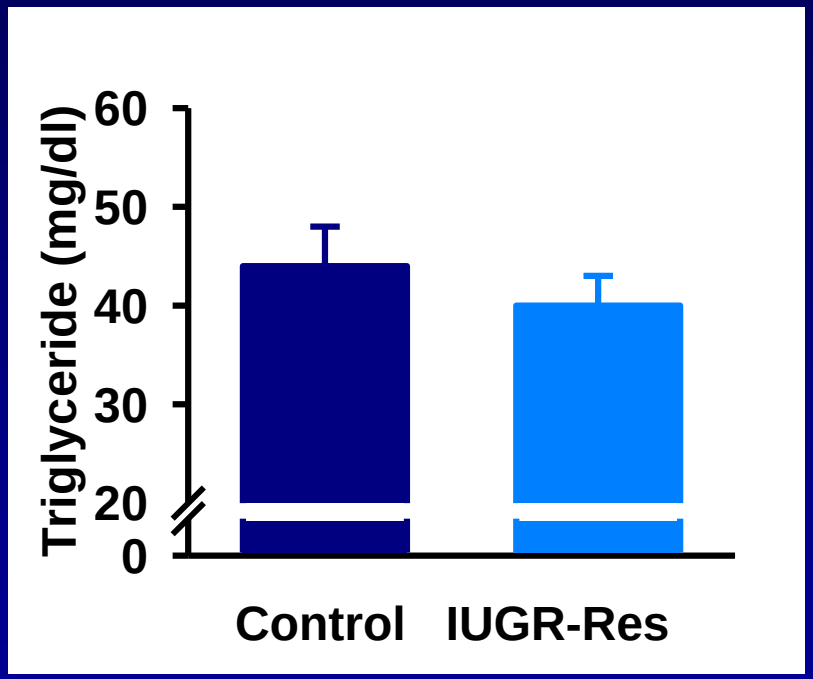
Normal Adult Body Fat

Mean ± SE; * p < 0.01

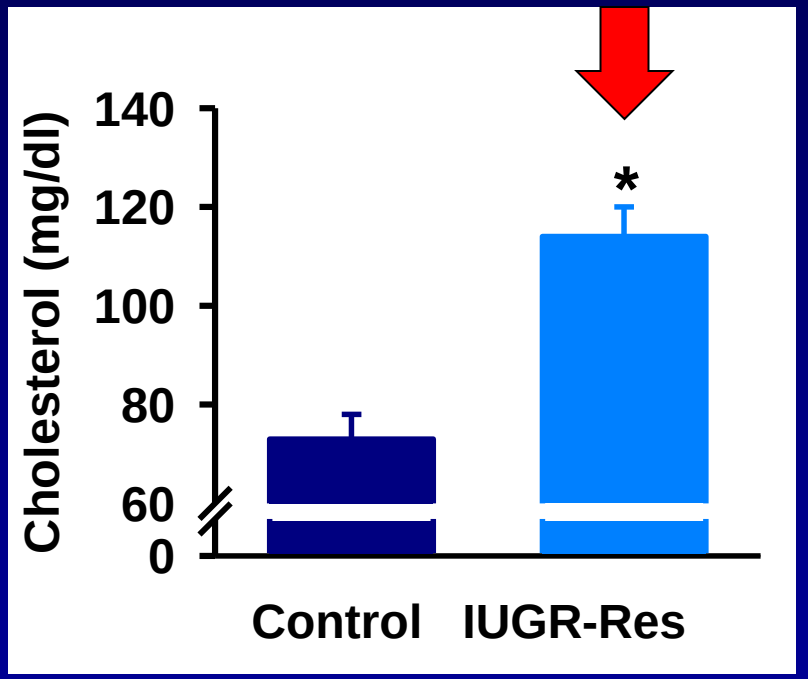
Desai et al, Am J Physiol, 2005

Lipid Profile
9 Month IUGR Non-obese Adult Males

Triglyceride



Cholesterol

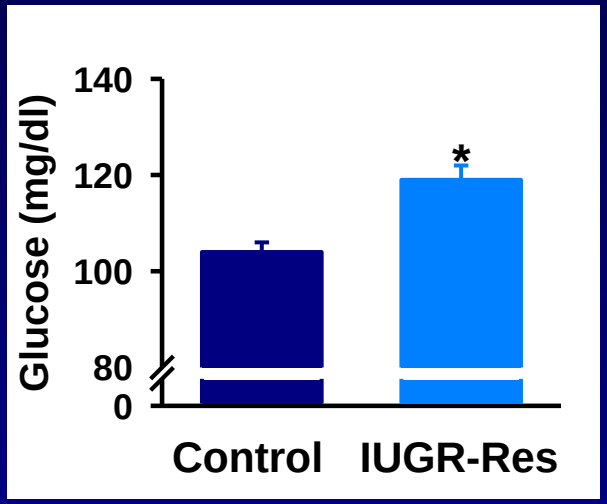


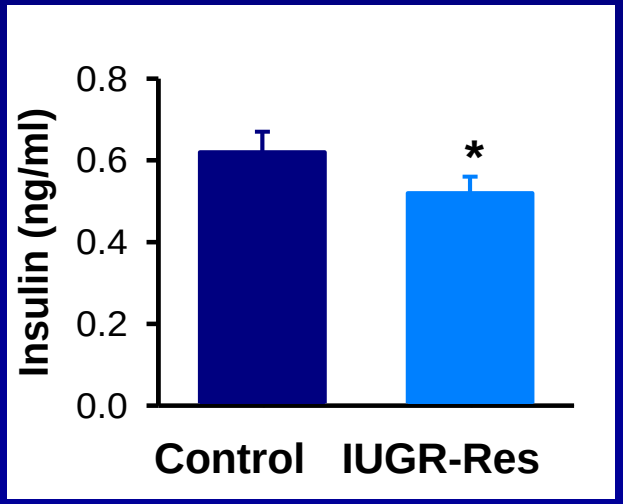
Hypercholesterolemia

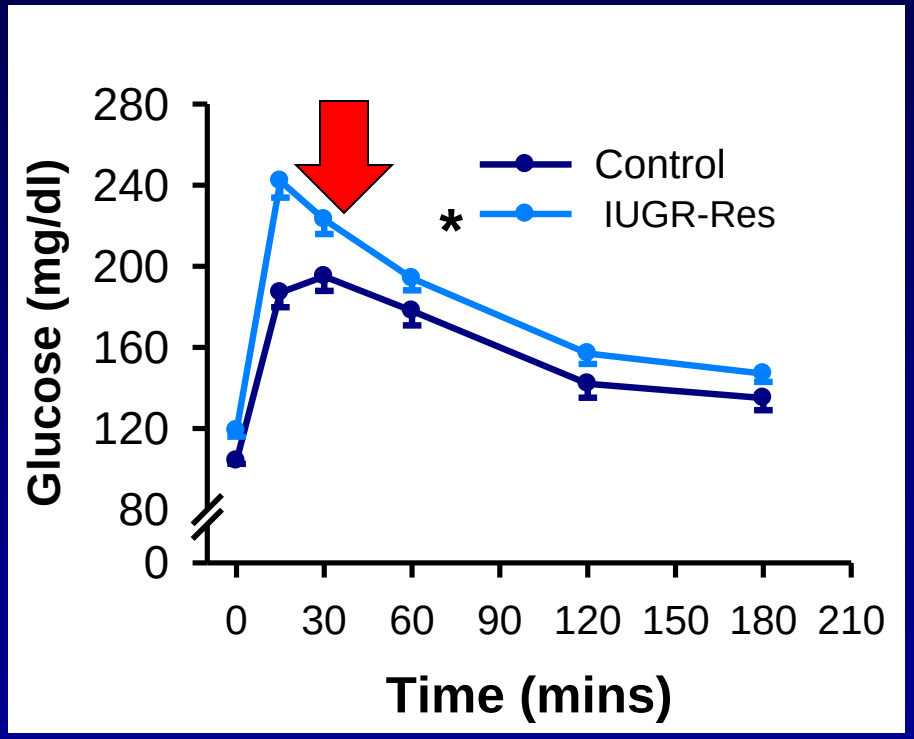
Mean ± SE; * p < 0.01

Desai et al, Am J Obstet Gynecol, 2007

Glucose, Insulin and GTT
9 Month IUGR Non-obese Adult Males







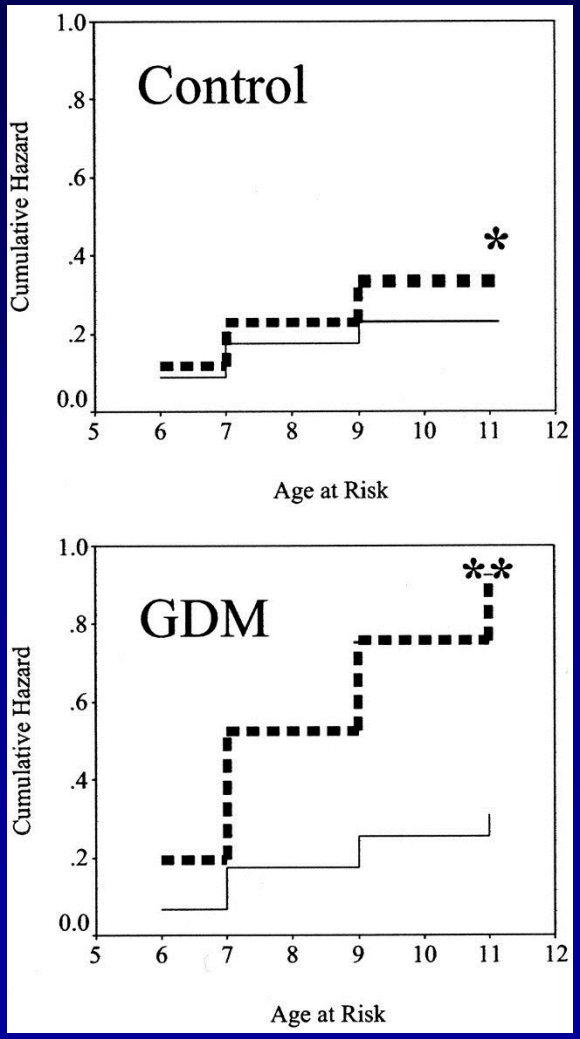
Insulin Insufficiency

Desai et al, Am J Obstet Gynecol, 2007

Summary: Adult Phenotype IUGR with Restricted Nursing

- Catch-up to control body weights without obesity
- Normal body fat and triglycerides
- Risk of Heart Disease
  - Increased cholesterol
  - Insulin insufficiency

Cumulative Risk for Child Metabolic Syndrome by Birth Weight



—— AGA

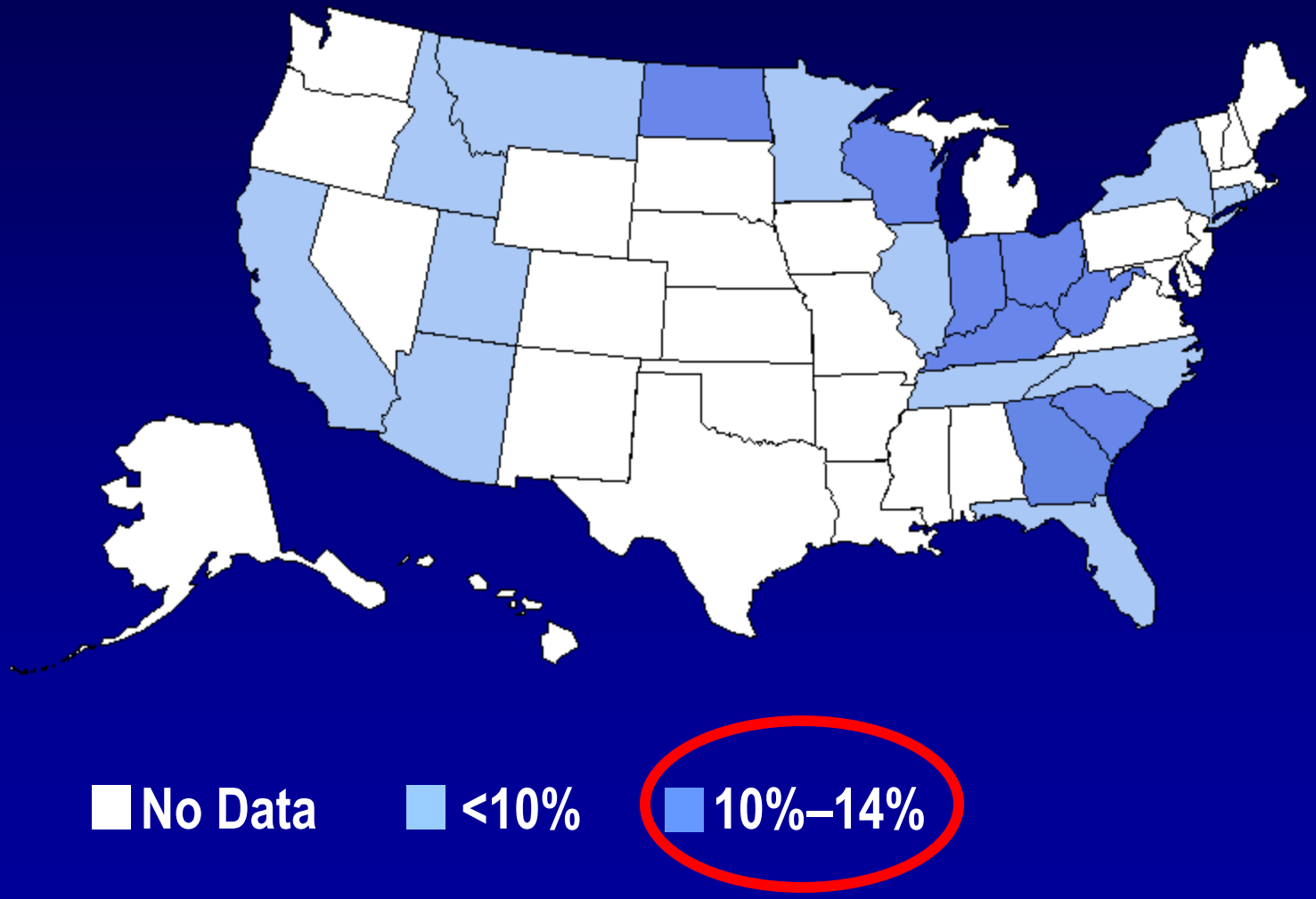
----- LGA

Charlotte M. Boney et al. Pediatrics 2005;115:e290-e296

Obesity Trends* Among U.S. Adults

CDC, 1985

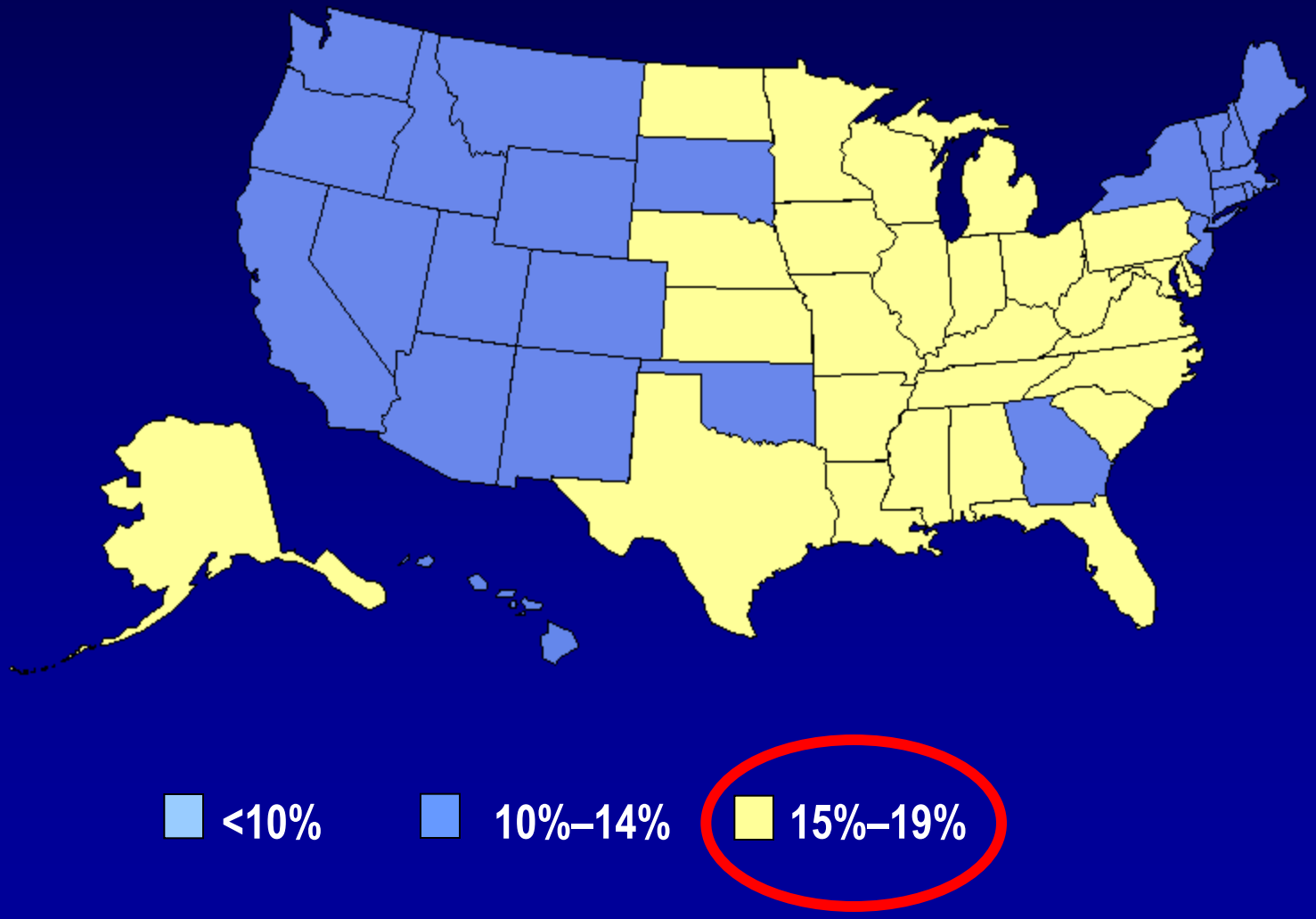
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

CDC, 1995

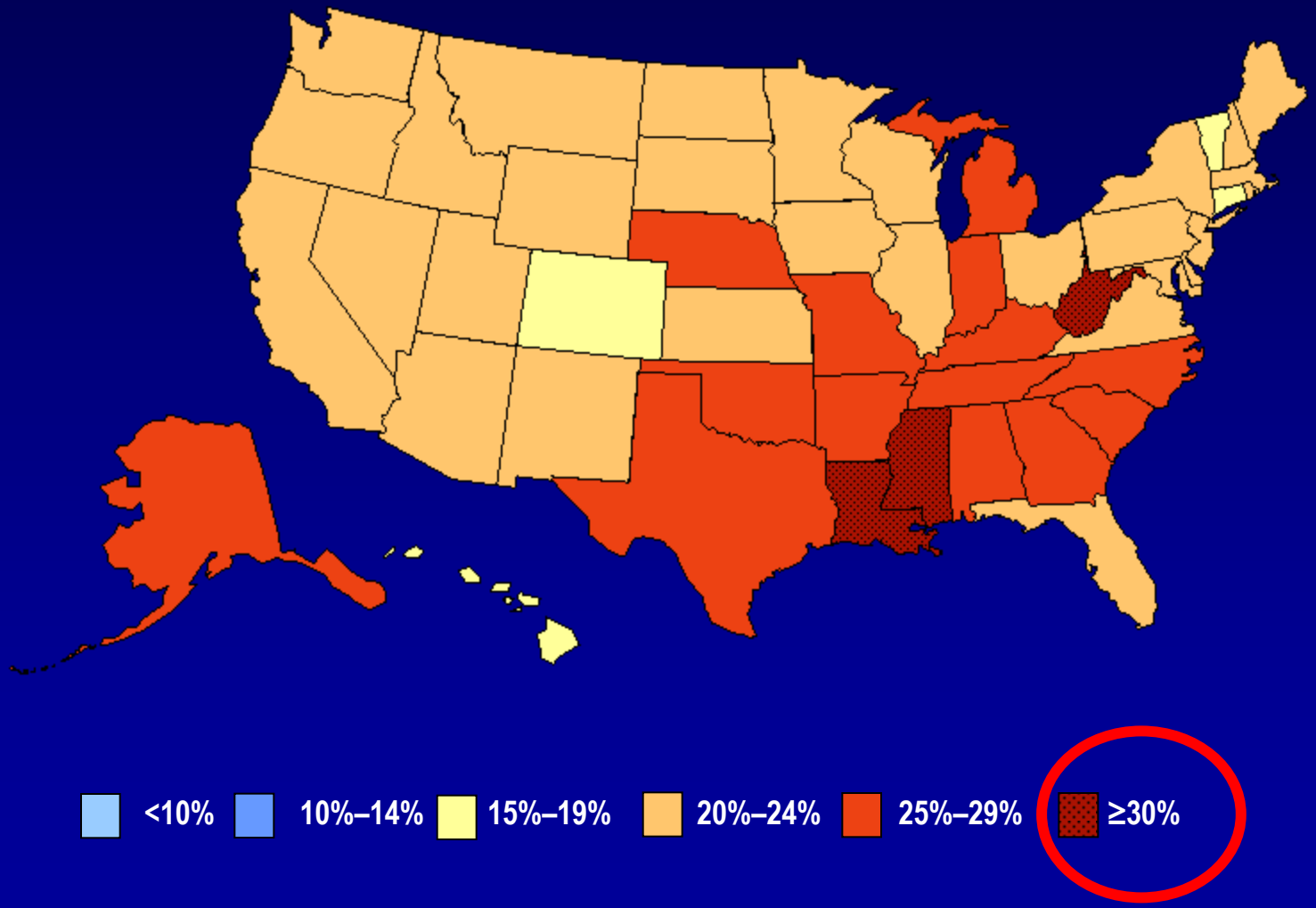
(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

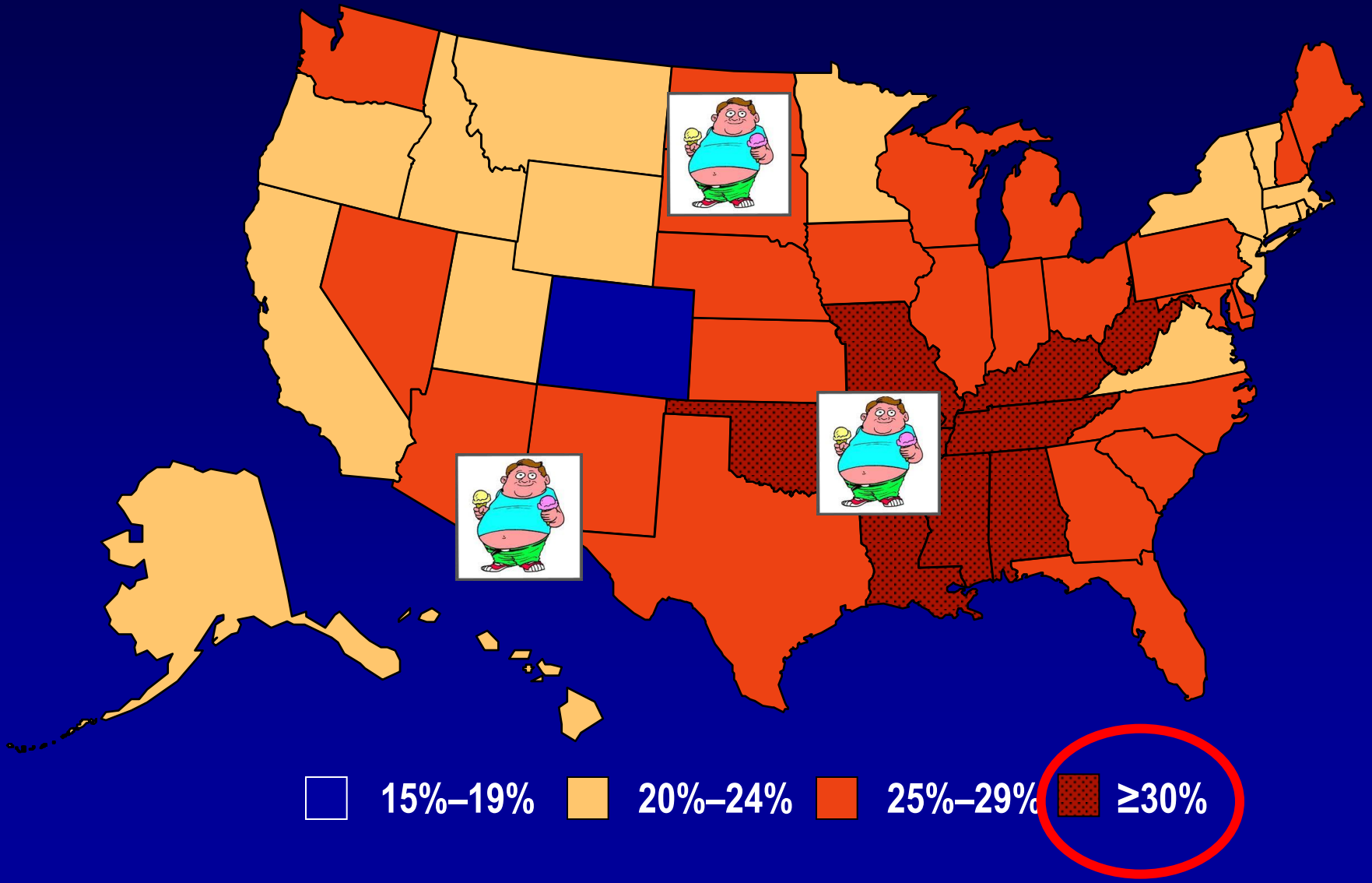
CDC, 2005

(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

CDC, 2009



Etiology of Obesity

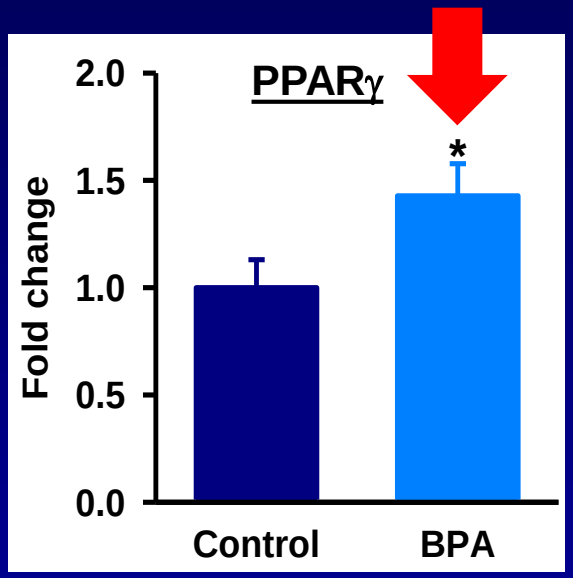
- Food Availability
  High Fat Diets

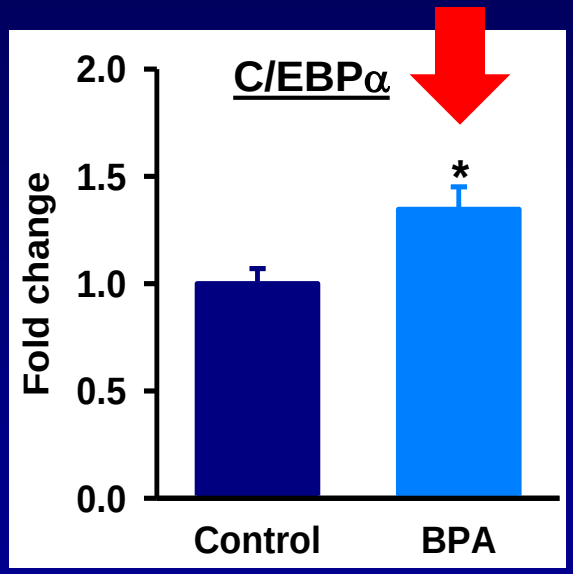
- Reduced Energy
  Expenditure

- Propensity for
  Obesity
- Developmental
  Programming

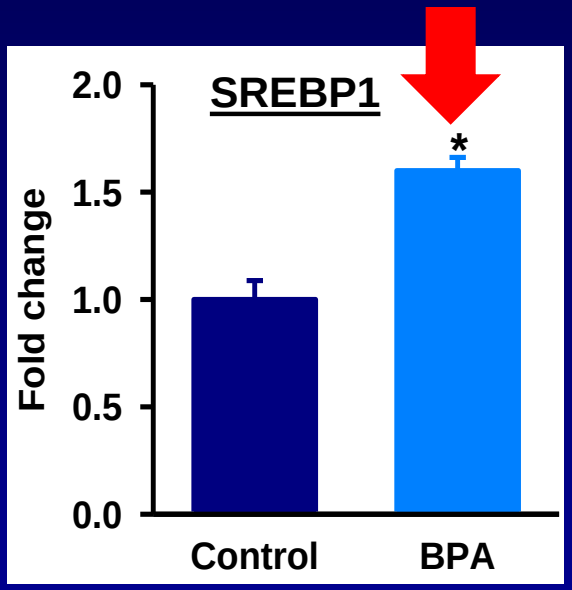
BPA: Adipocyte Transcription Factors

Adipogenic



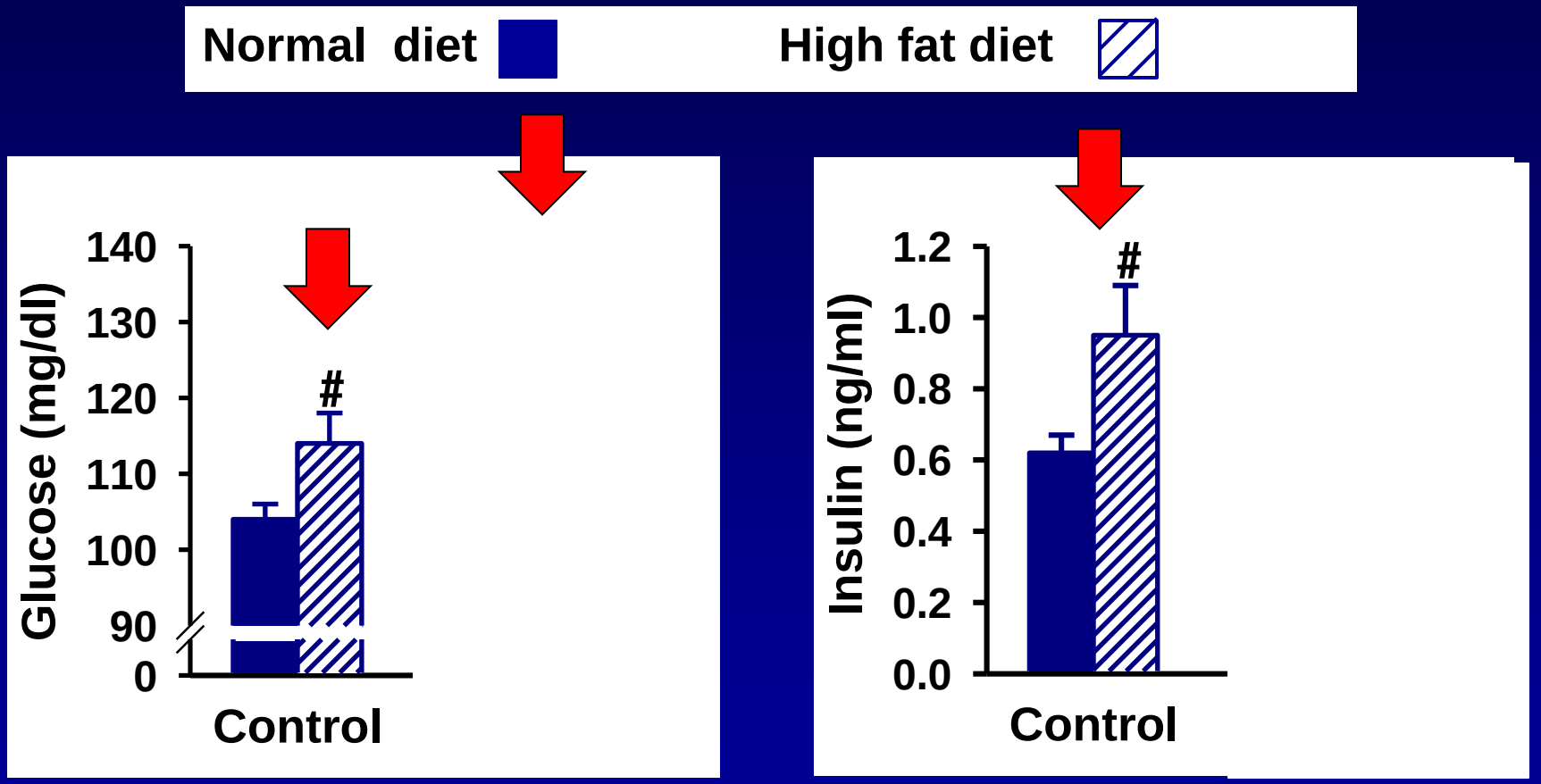


Lipogenic



Increased Adipocyte Differentiation and Lipogenesis

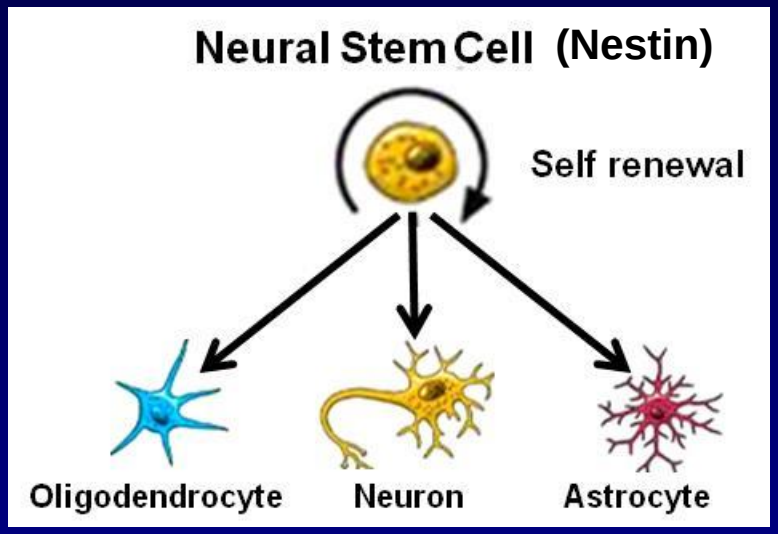
Postnatal High Fat Diet
Glucose and Insulin

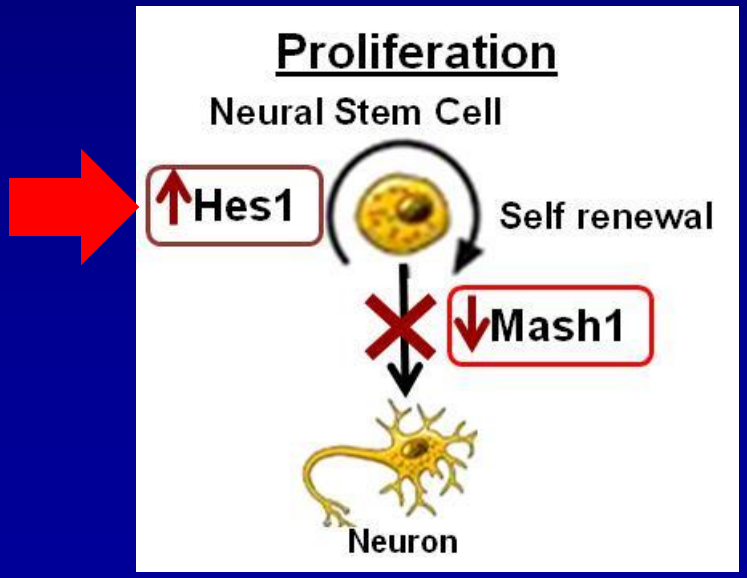


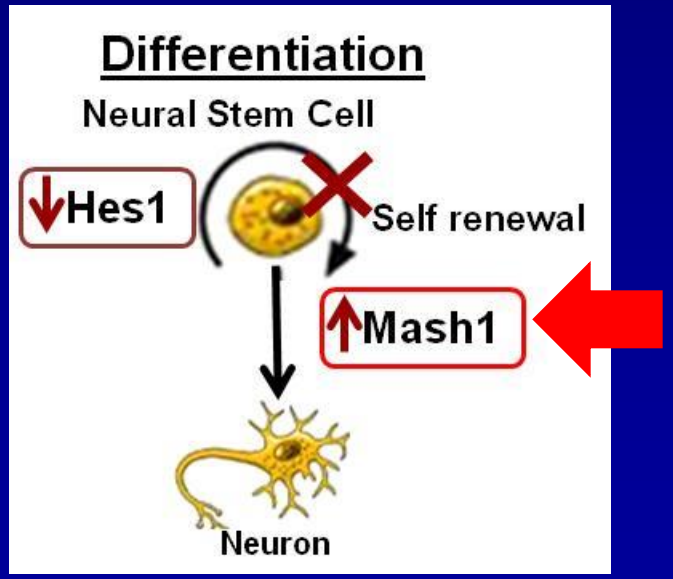
*** vs Control; # vs High Fat Diet**

Desai et al, AJP, 2007

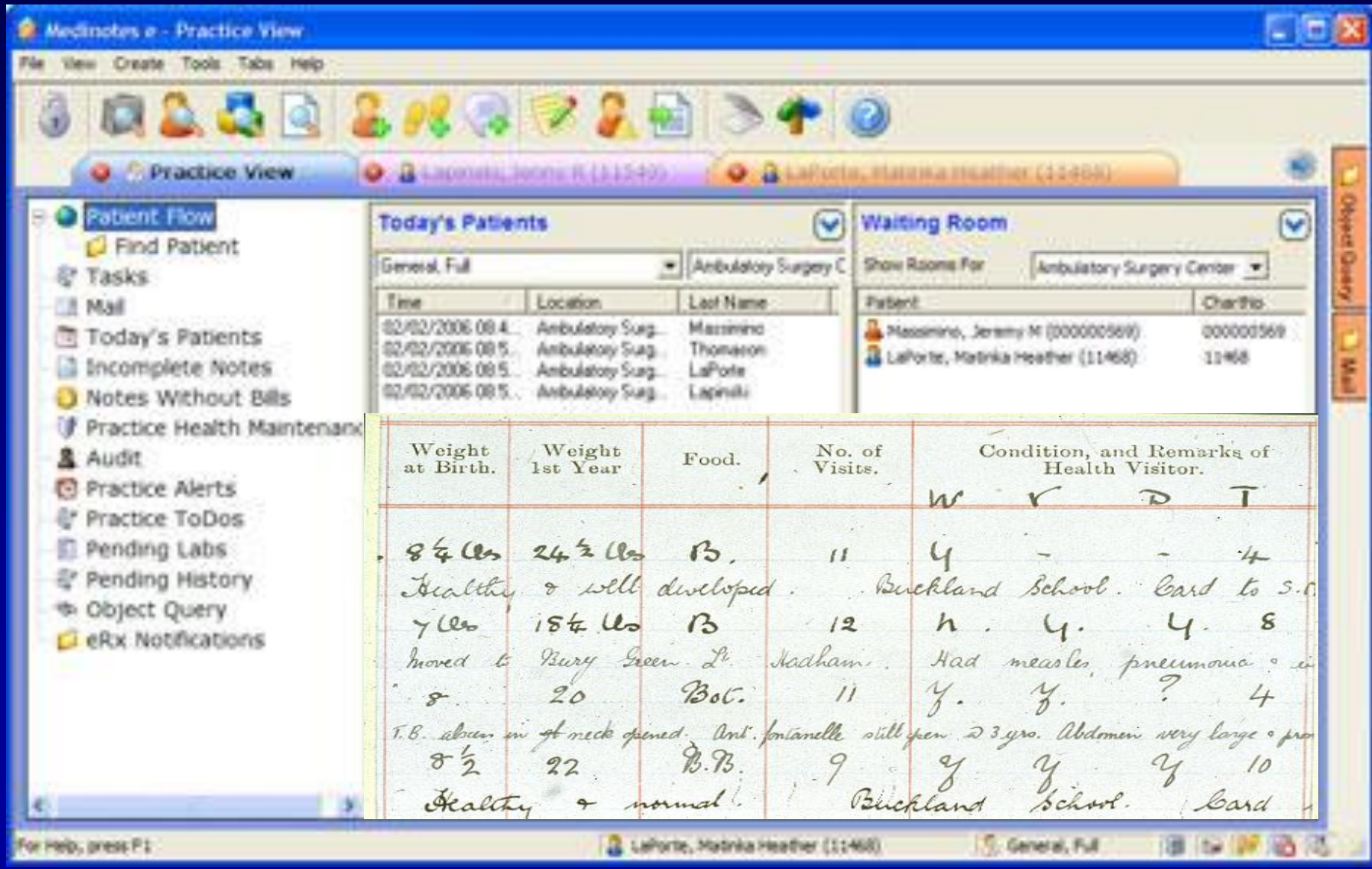
NSC Proliferative & Differention Factors



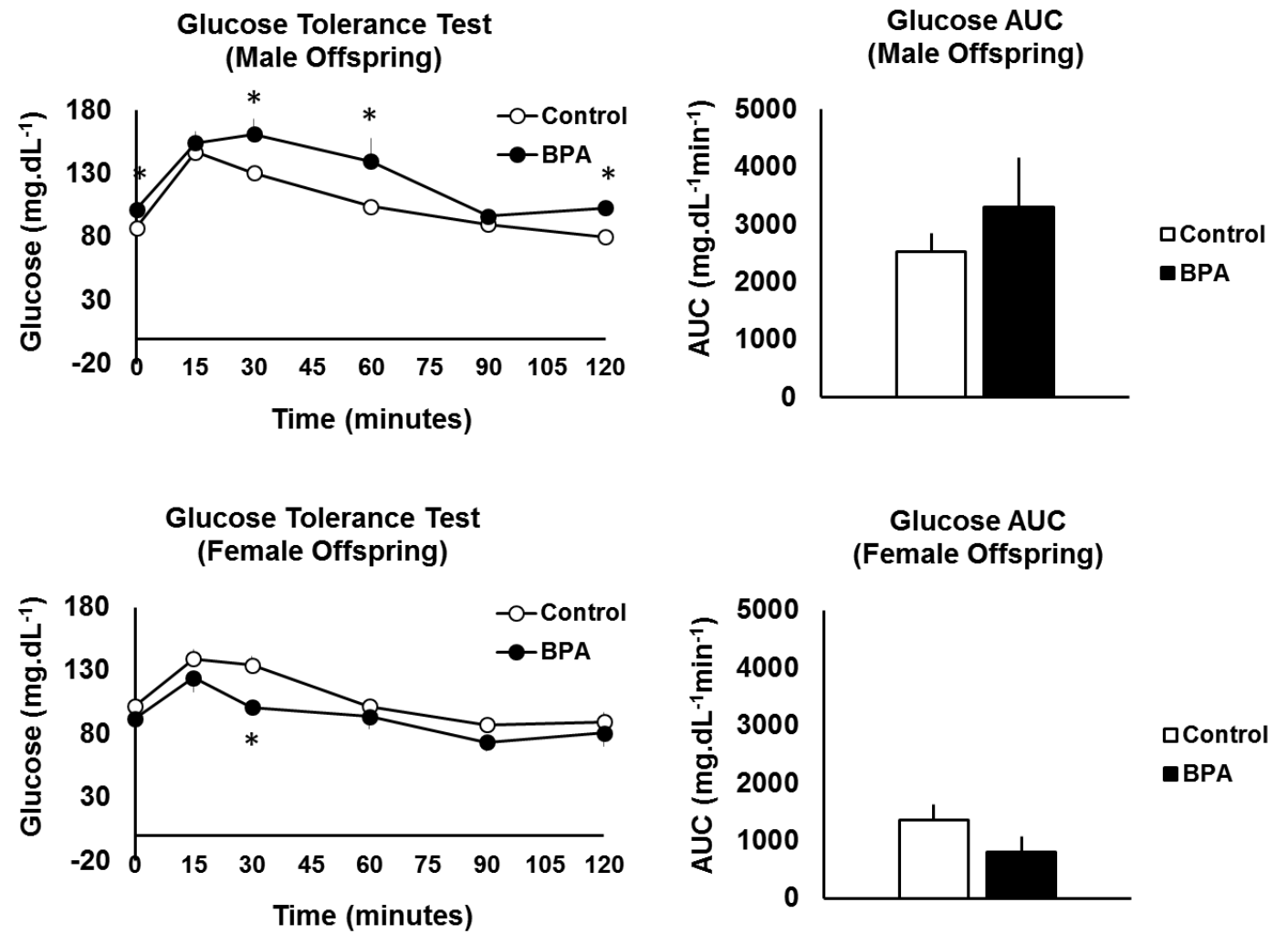




Electronic Medical Record

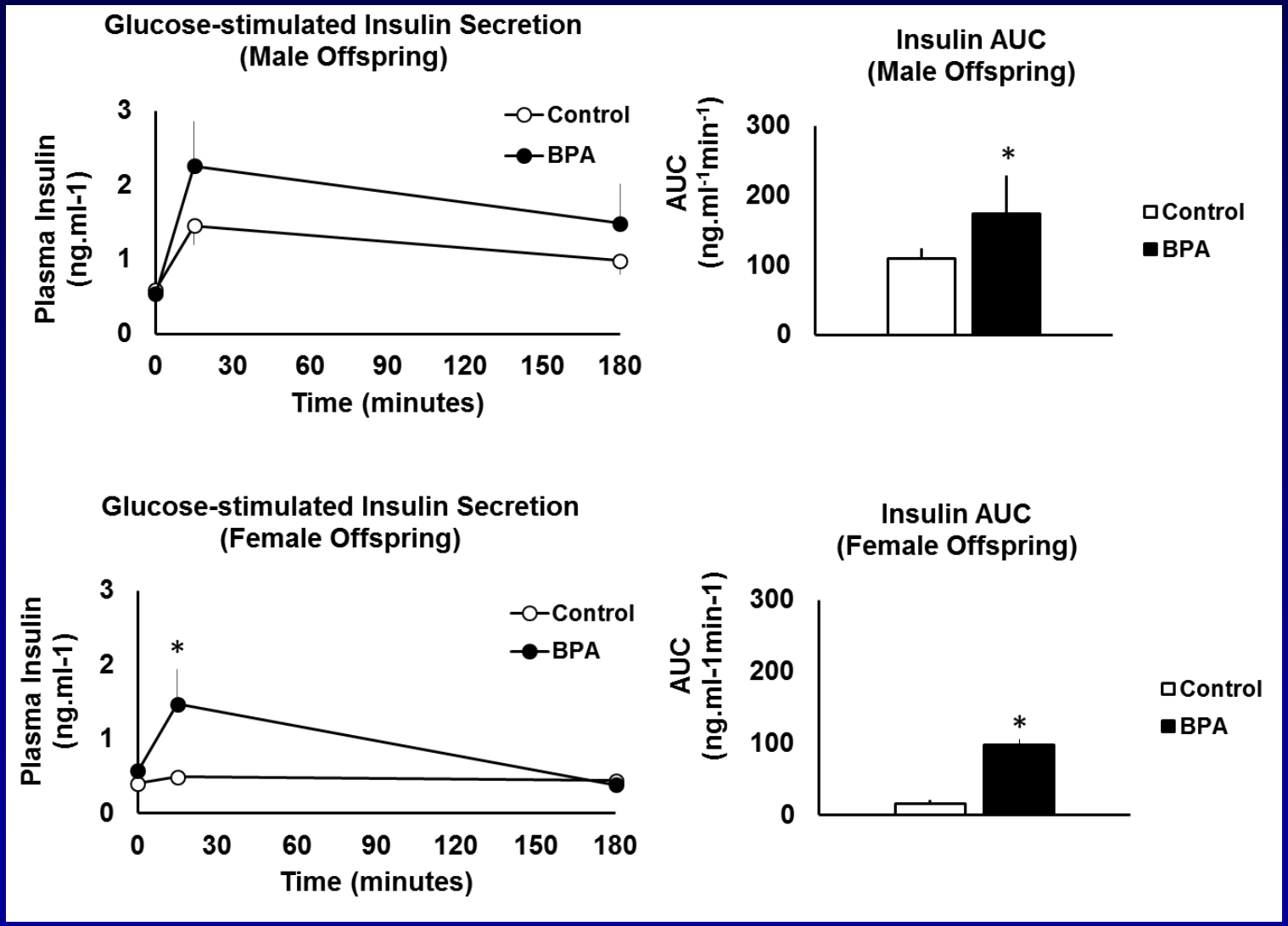


Offspring Glucose Tolerance at 6 Months



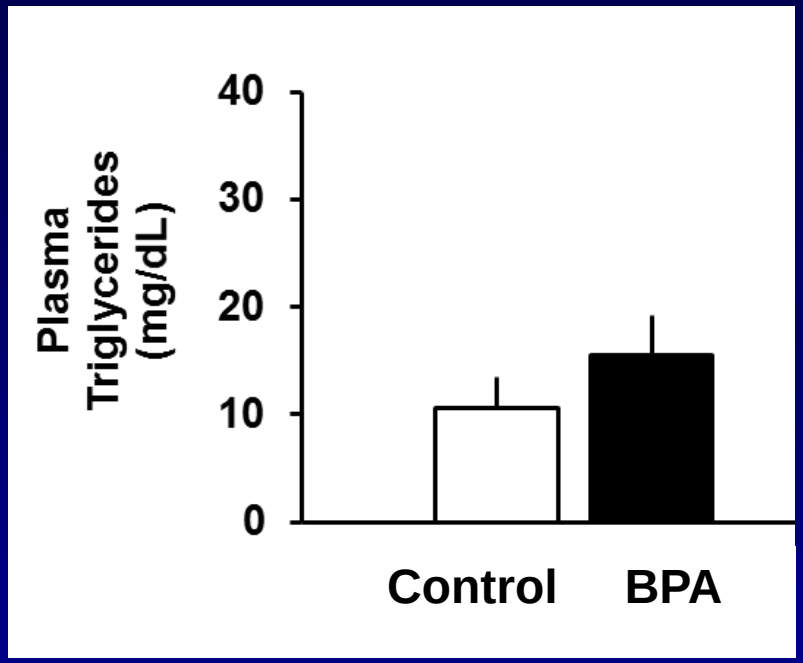
Impaired Glucose Tolerance in Males

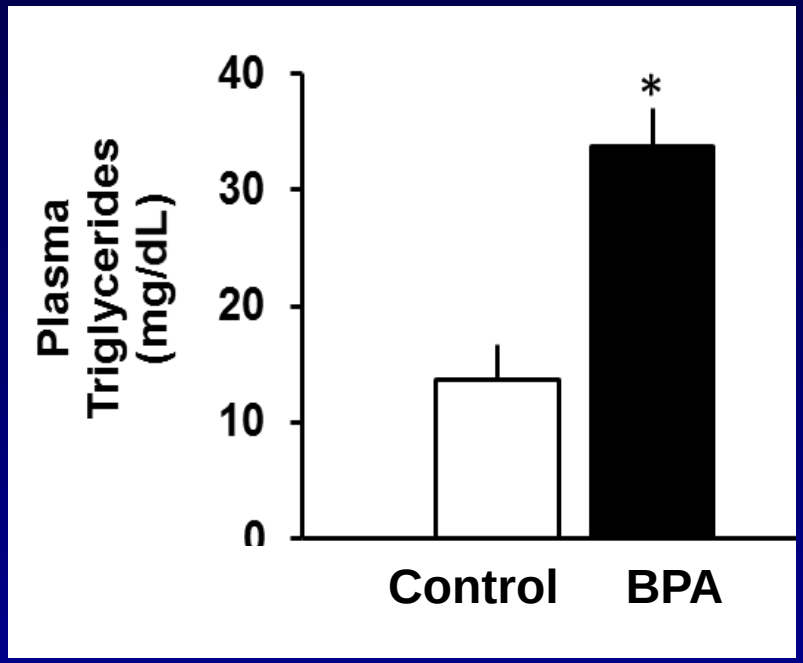
Offspring Glucose-Stimulated Insulin Secretion 6 Months



Increased Insulin Secretion in Males and Females

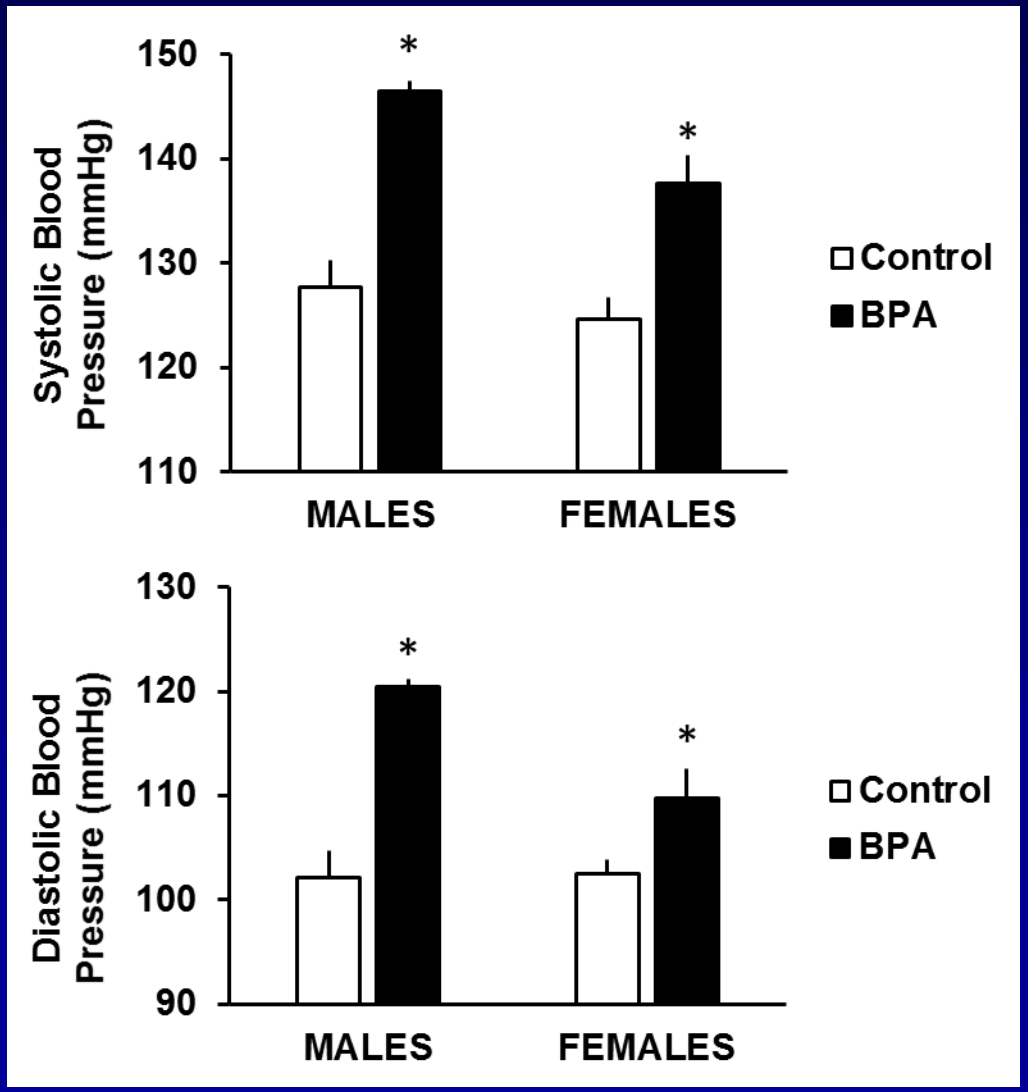
Offspring Triglycerides at 6 Months





Hypertriglyceridemia in Females

Offspring Blood Pressure at 6 Months



Hypertension in Males and Females

Programming vs. Mutations

Genetic mutations: Long epochs, irreversible

Programmed phenotypes: Respond to acute environmental stresses

Environmental Stresses on Survival
Drought and Famine

- **Famine**: nutrient reduction

Famine/drought during pregnancy results in low birth weight infants

"Thrifty Phenotype"

- **Increased food intake, gorging**
- **Efficient metabolism**
- **Reduced energy expenditure**

Survival Advantage in an environment of reduced nutrient availability

“Thrifty” vs. “Inadvertent Thrifty” Phenotype

- **Intrauterine Growth Restricted Newborns**
  - **Improved Fecundity:**
    - **Maternal medical illness**
  - **Etiologies:**
    - **Substance abuse, cigarette smoking**
  - **Twins and higher order:**
    - **Natural and In Vitro Fertilization**

- **Enhanced Neonatal Survival: viability 400 g**

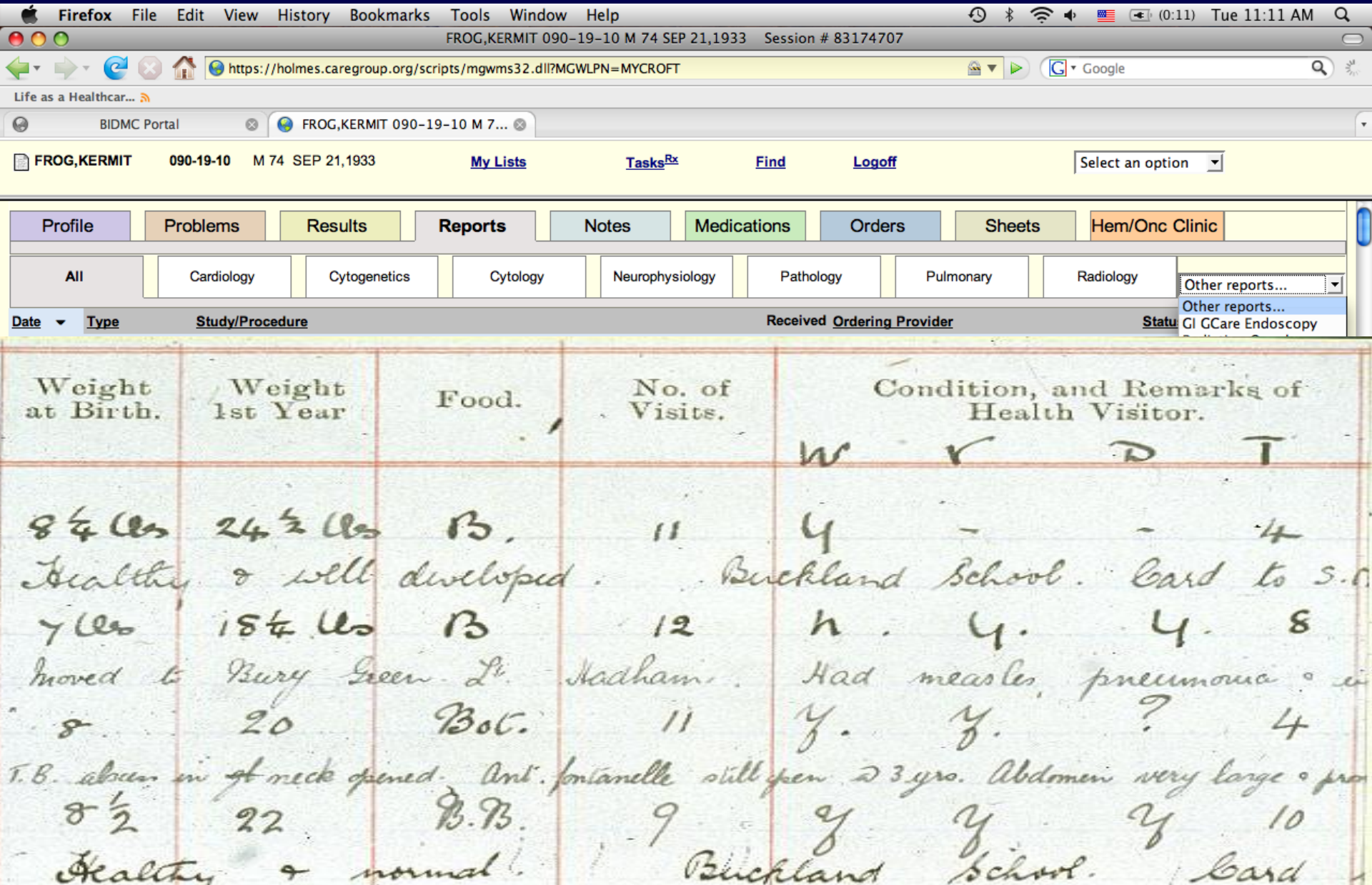
High fat, high calorie diet

Thrifty Phenotype → **Obesity**

Hertfordshire Birth Records 1911-1949

Weight at Birth.	Weight 1st Year	Food.	No. of Visits.	Condition, and Remarks of Health Visitor. W	V	D	T
8¼ lbs	24½ lbs	B.	11	4	-	-	4
Healthy & well developed.				Buckland School. Card to S.C.			
7 lbs	18¼ lbs	B	12	h.	4.	4.	8
moved to Bury Green Lr.			Hadham.	Had measles, pneumonia & ear			
8	20	Bot.	11	4.	4.	?	4
T.B. abscess in left neck opened. Ant. fontanelle still open @ 3 yrs. Abdomen very large & pro							
8½	22	B.B.	9	4	4	4	10
Healthy & normal.				Buckland School. Card			

Electronic Medical Record



Weight at Birth.	Weight 1st Year	Food.	No. of Visits.	Condition, and Remarks of Health Visitor. W	R	D	T
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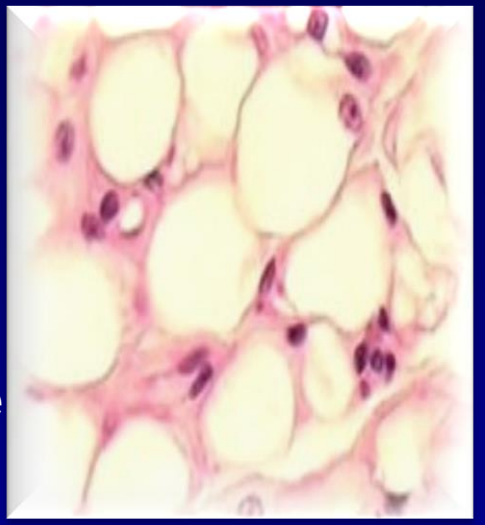
7 lbs	18¼ lbs	B	12	h.	4.	4.	8
Moved to Bury Green Lt. Hadham. Had measles, pneumonia &							
8	20	Bot.	11	Y.	Y.	?	4
T.B. abscess in rt neck opened. Ant. fontanelle still open @ 3 yrs. Abdomen very large & pro							
8½	22	B.B.	9	Y	Y	Y	10
Healthy & normal. Buckland School. Card							

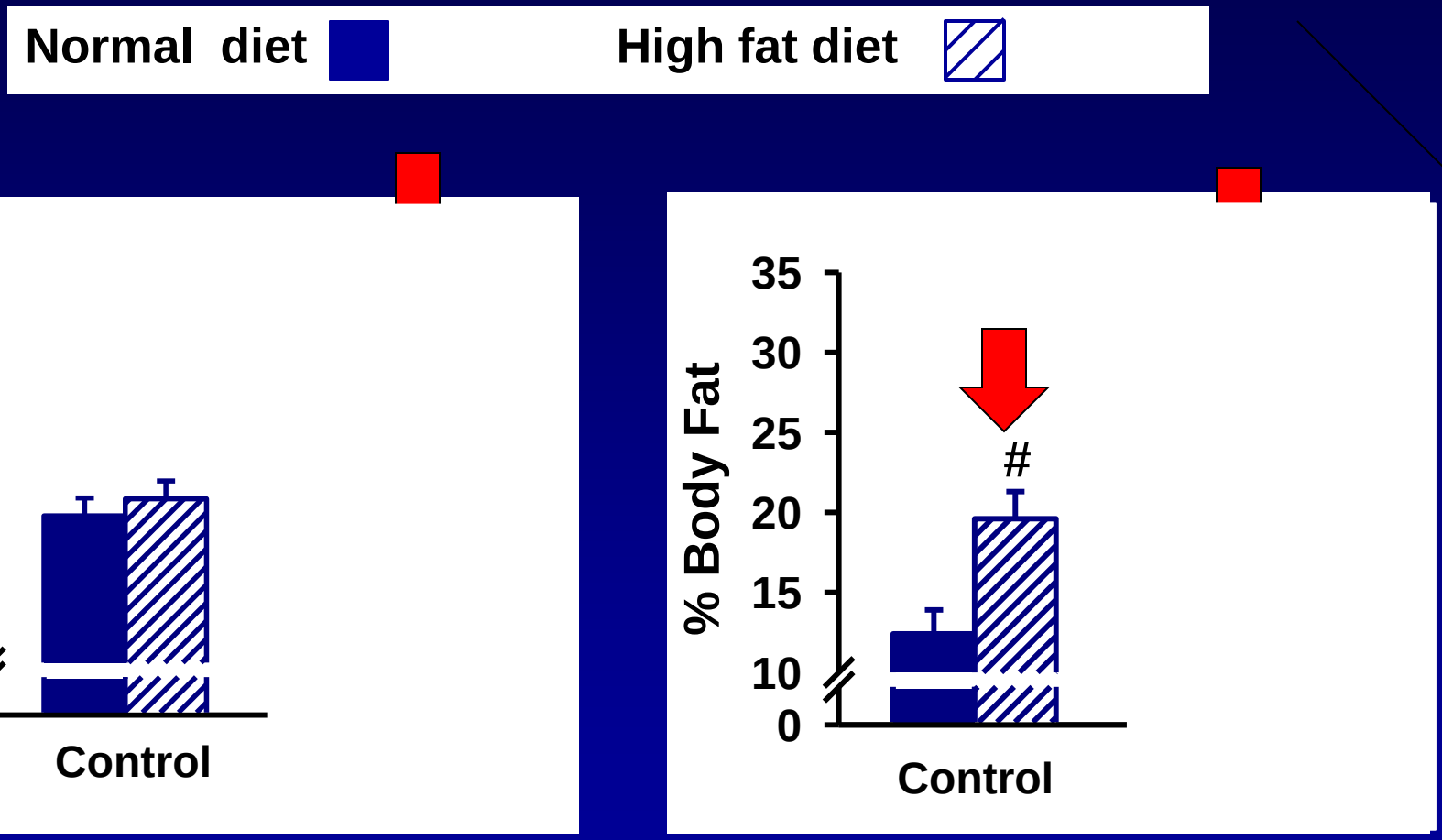
High Fat Diet

Increased fat storage



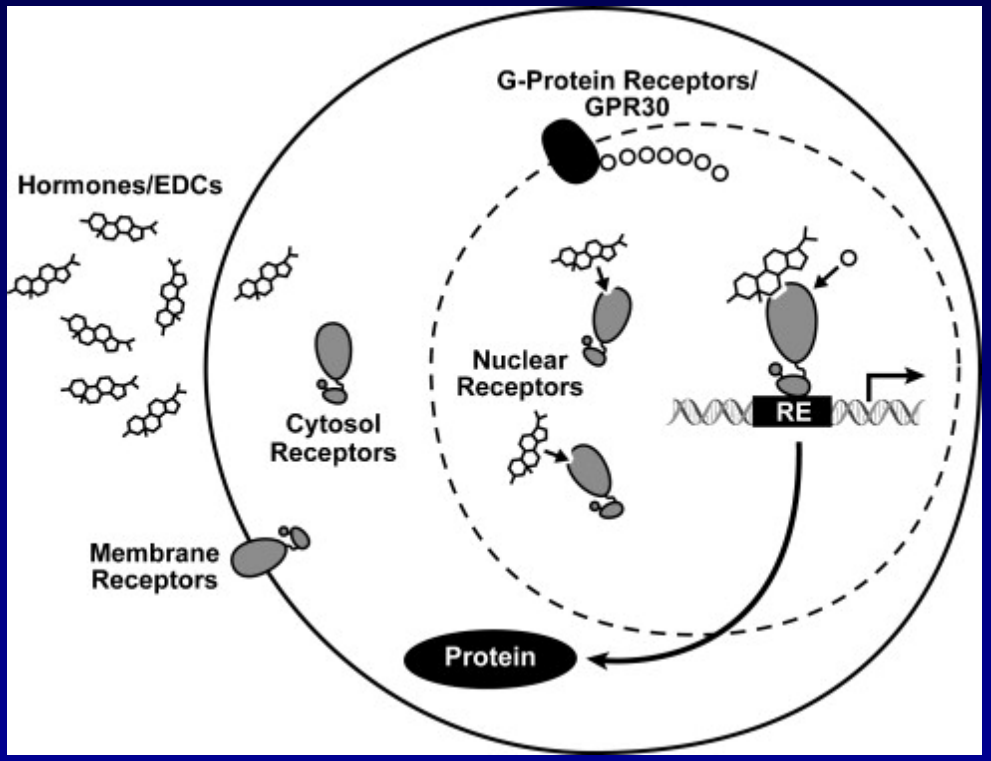
Non-alcoholic fatty liver disease

Postnatal High Fat Diet
Body Composition: Controls and IUGR

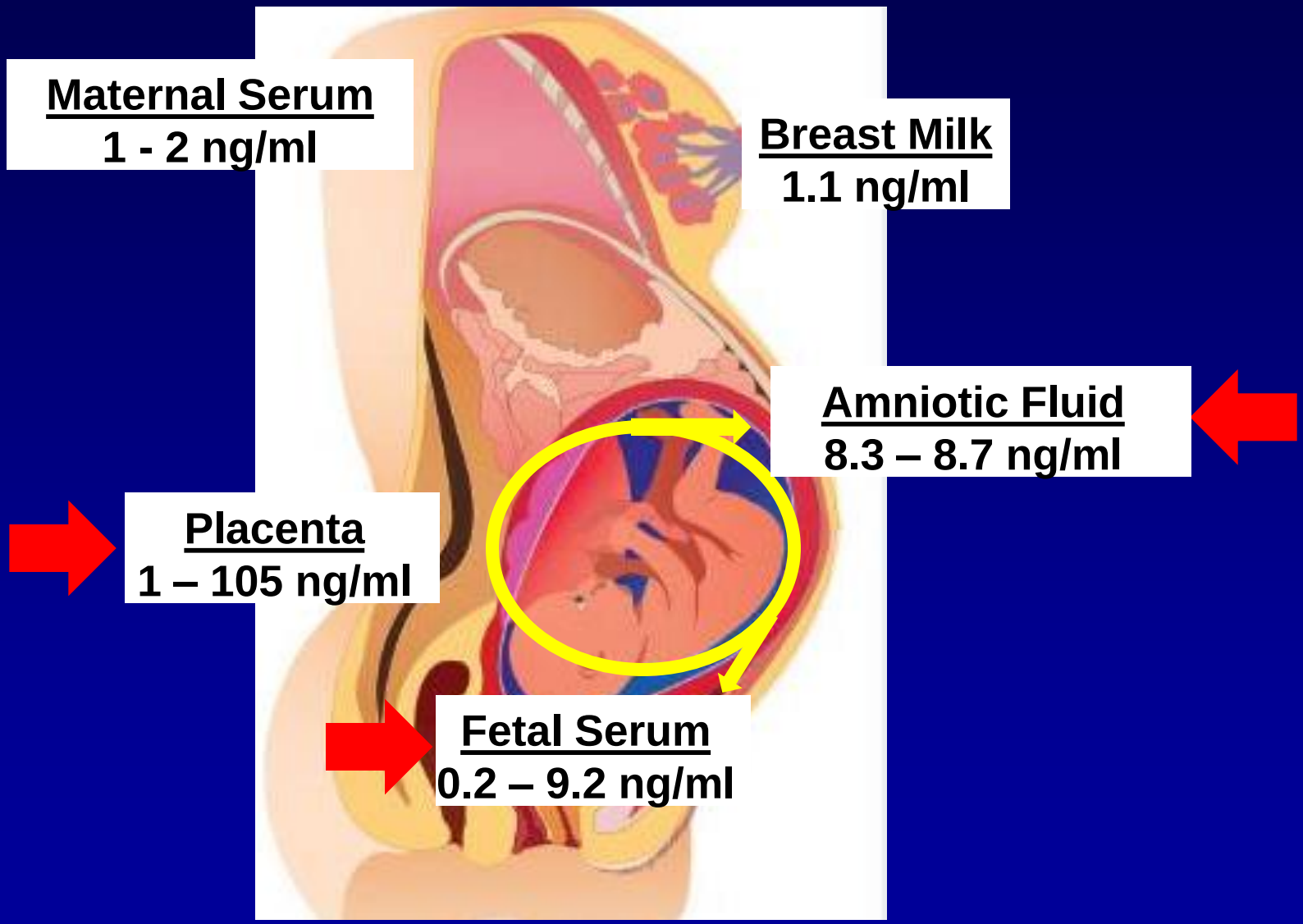


* vs Control; # vs High Fat Diet

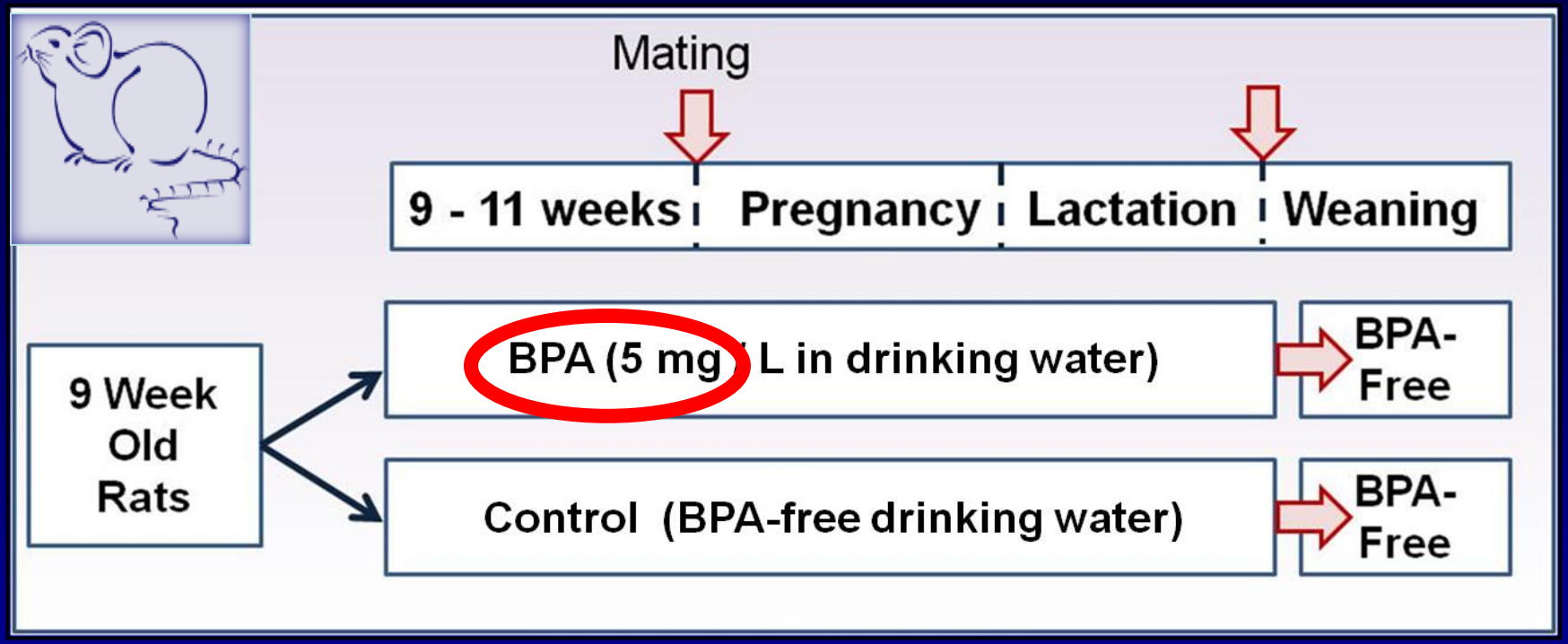
Bisphenol A (BPA)



NHANES: BPA Levels during Pregnancy



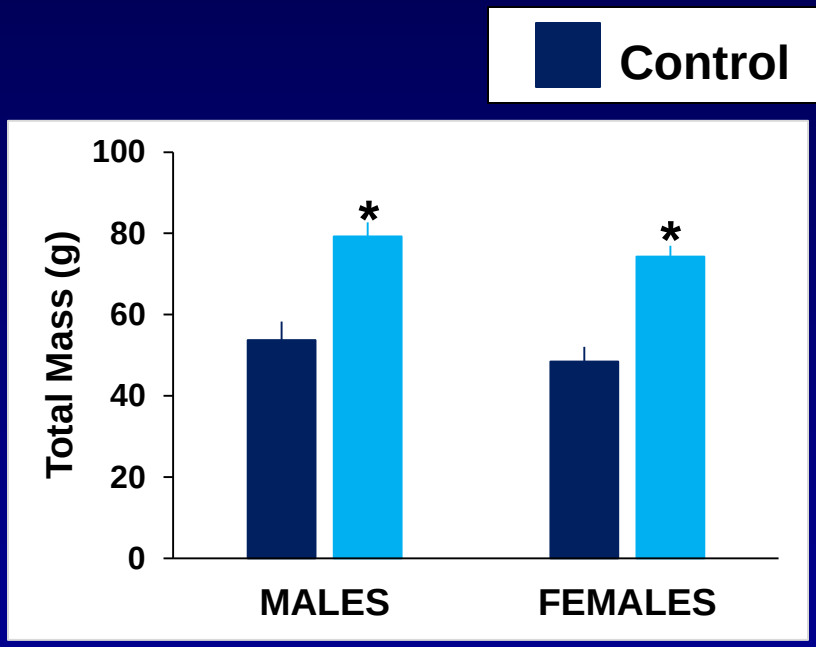
Model of Maternal Bisphenol A (BPA)

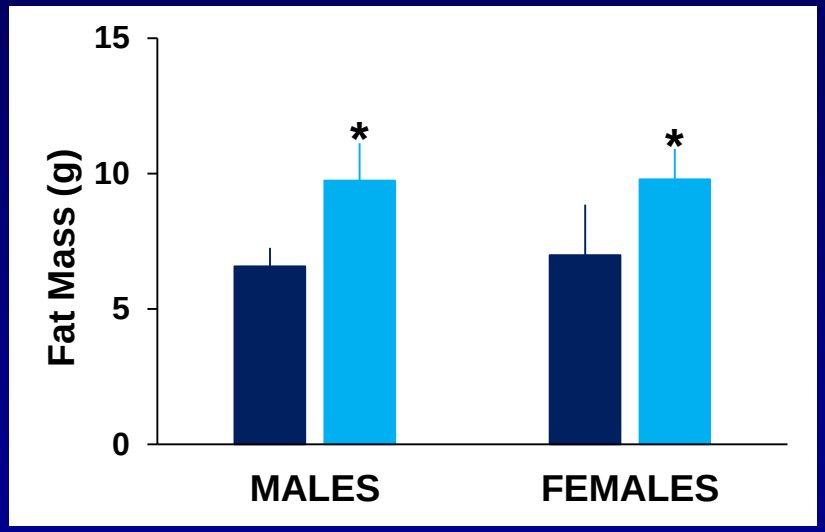


OFFSPRING

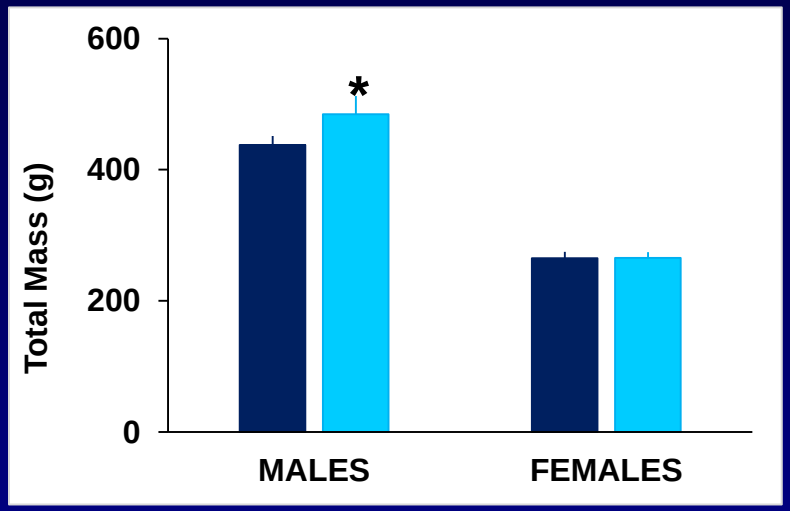
- **Litter size:** Culled to 4 males and 4 females at birth
- **Nursing:** All pups nursed by same dams until p21
- **Weaning:** At p21 to ad libitum food and BPA-free water

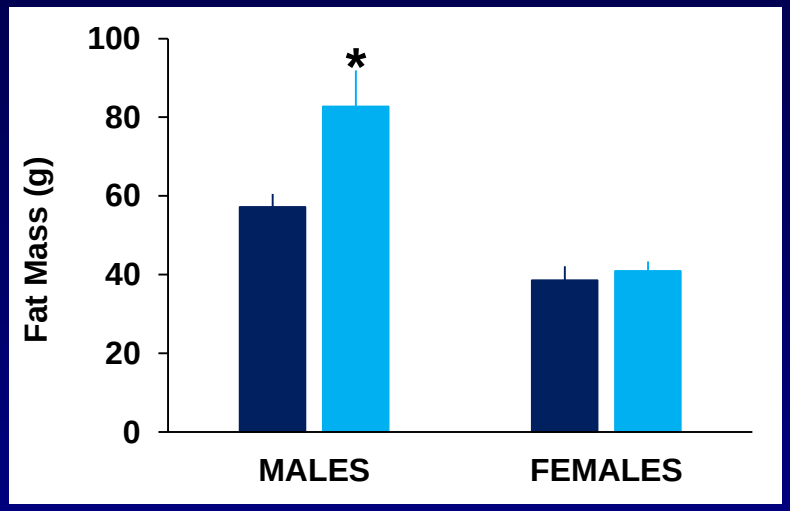
Offspring Body Composition at 3 Weeks

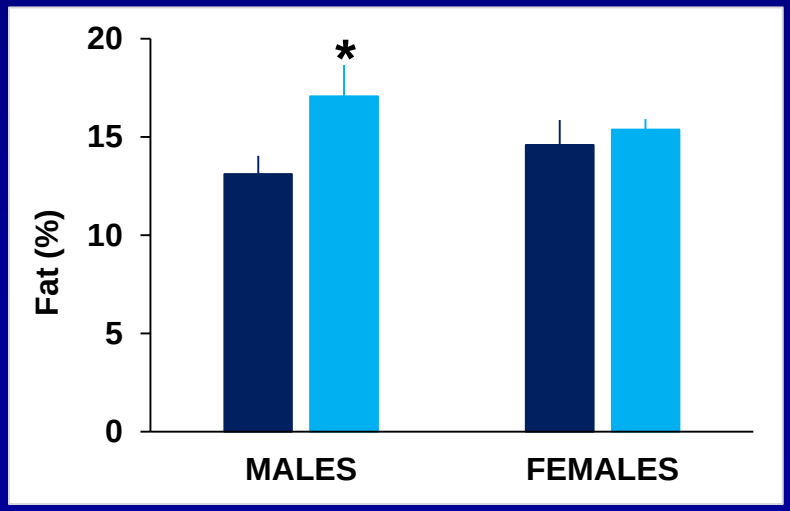




Offspring Body Composition at 6 months



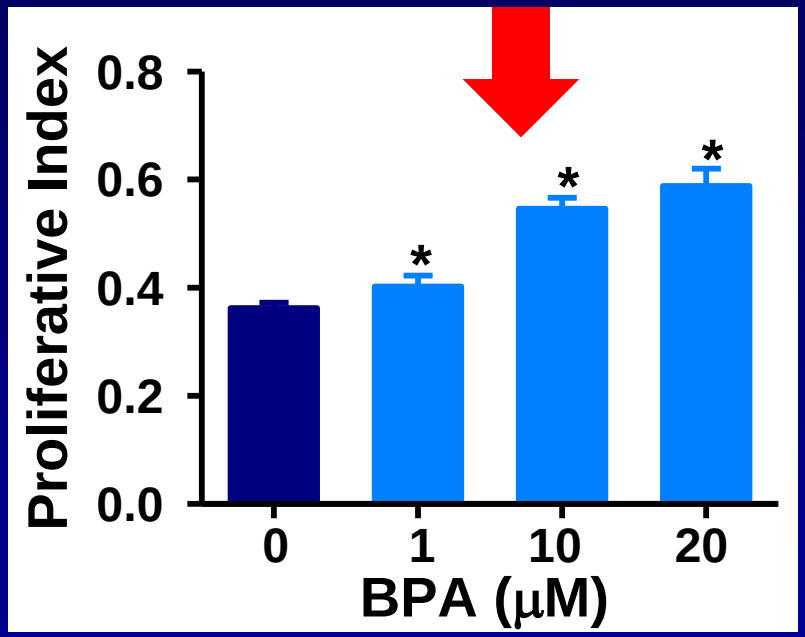




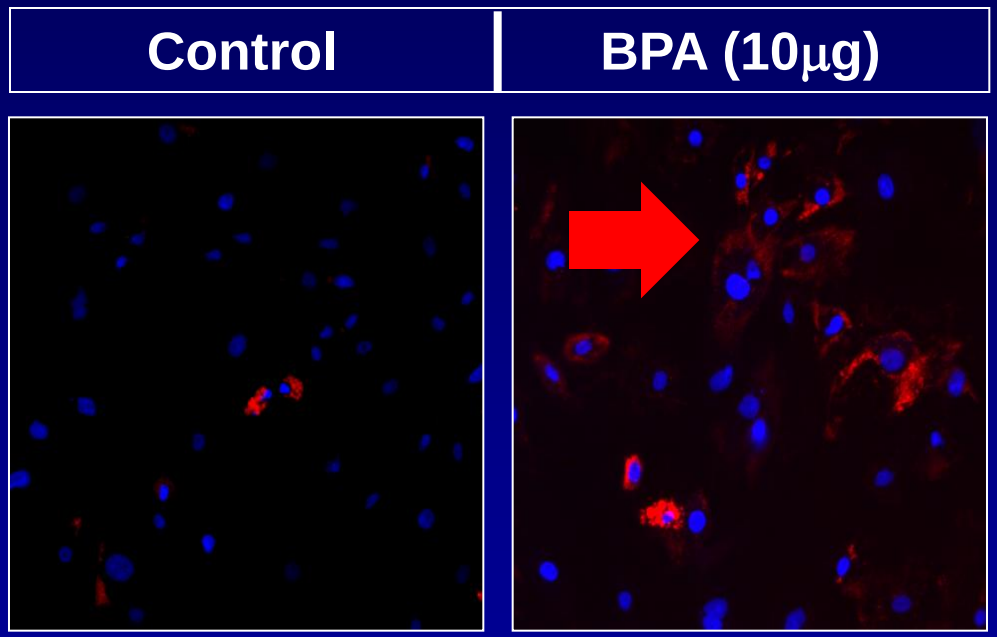
Increased Body Fat in Males

BPA: Preadipocytes

Adipogenesis

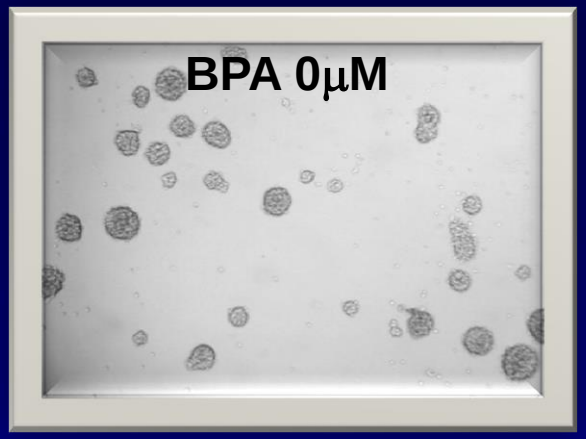


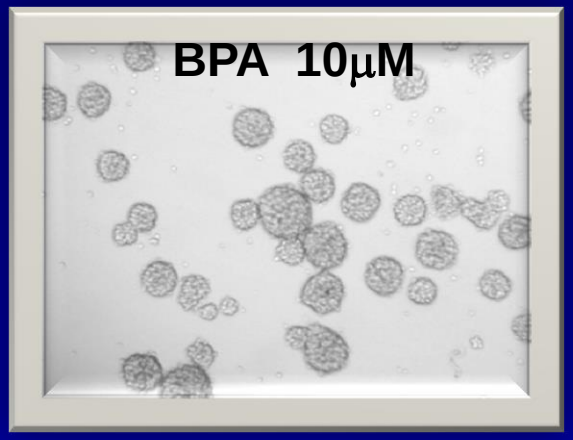
Lipogenesis

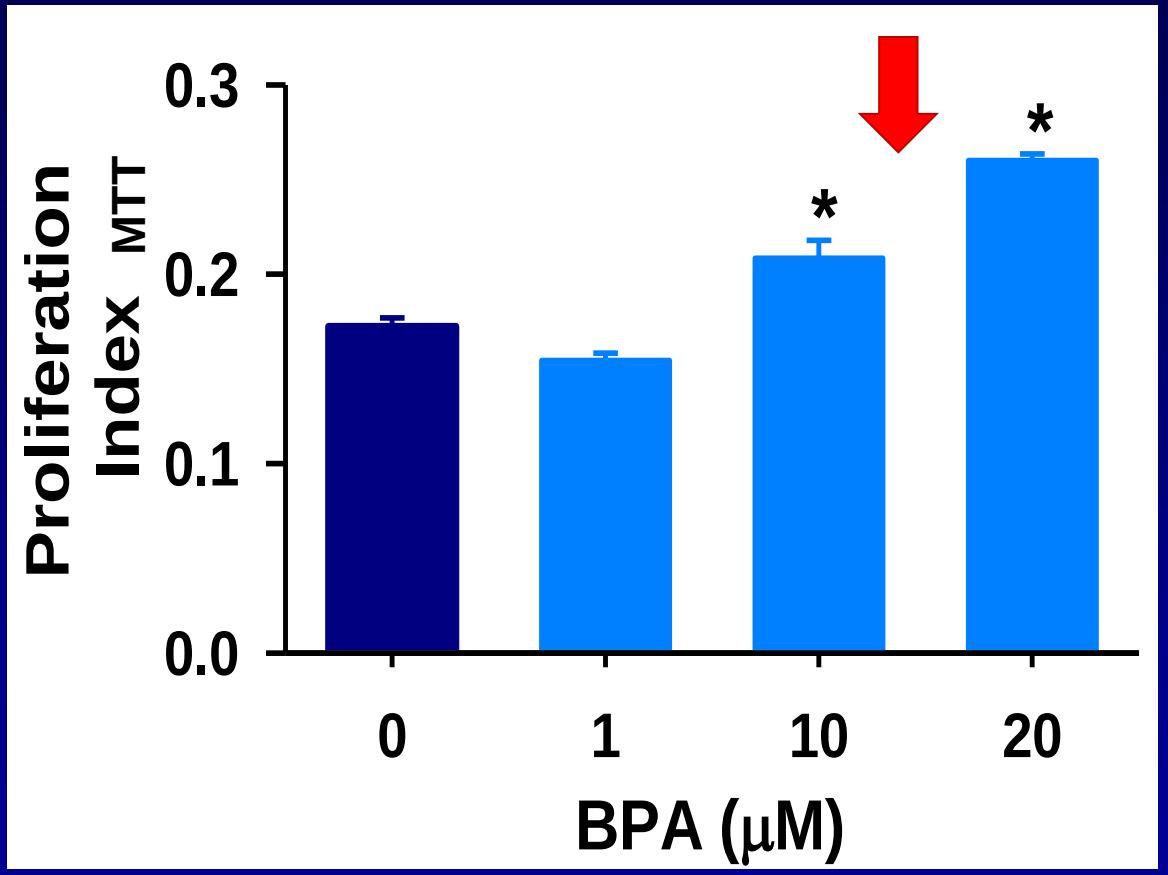


Increased Proliferation and Lipid Storage

BPA: Neural Stem Cell Proliferation





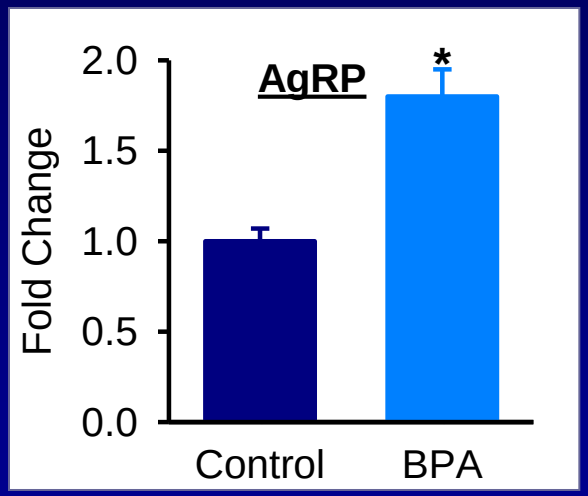


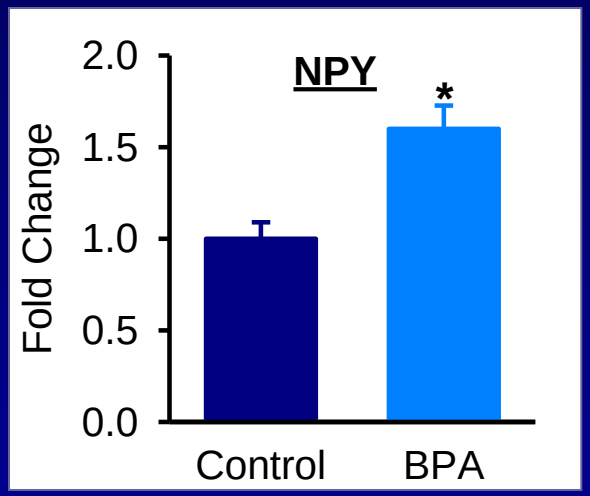
Increased Proliferation

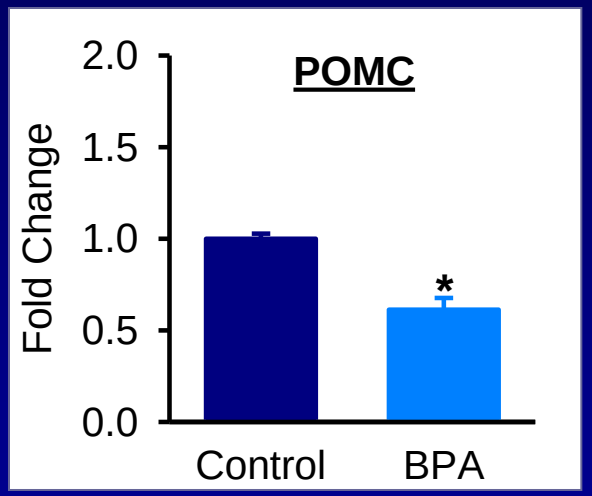
BPA Neural Stem Cell Differentiation

Appetite

Satiety



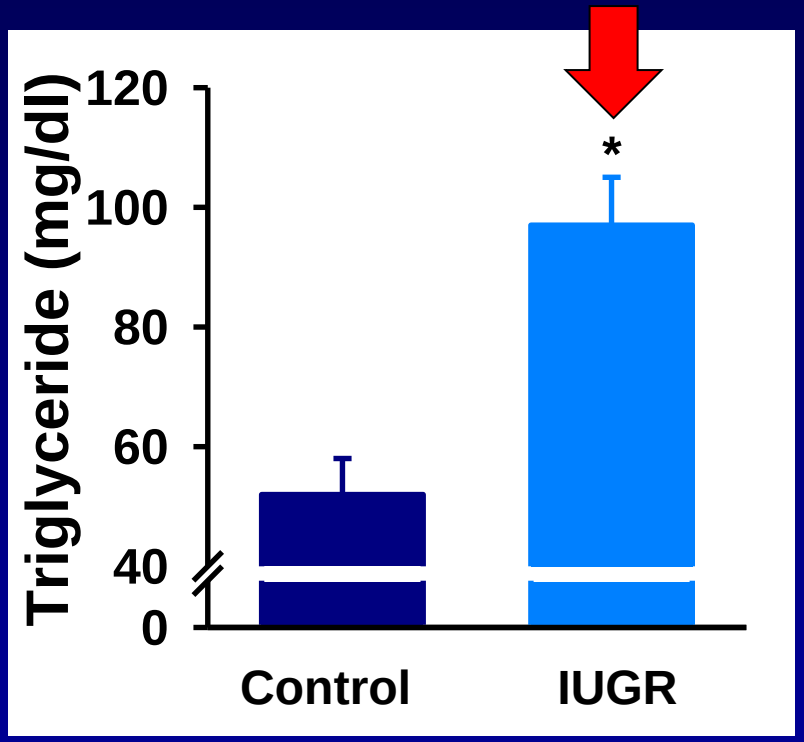




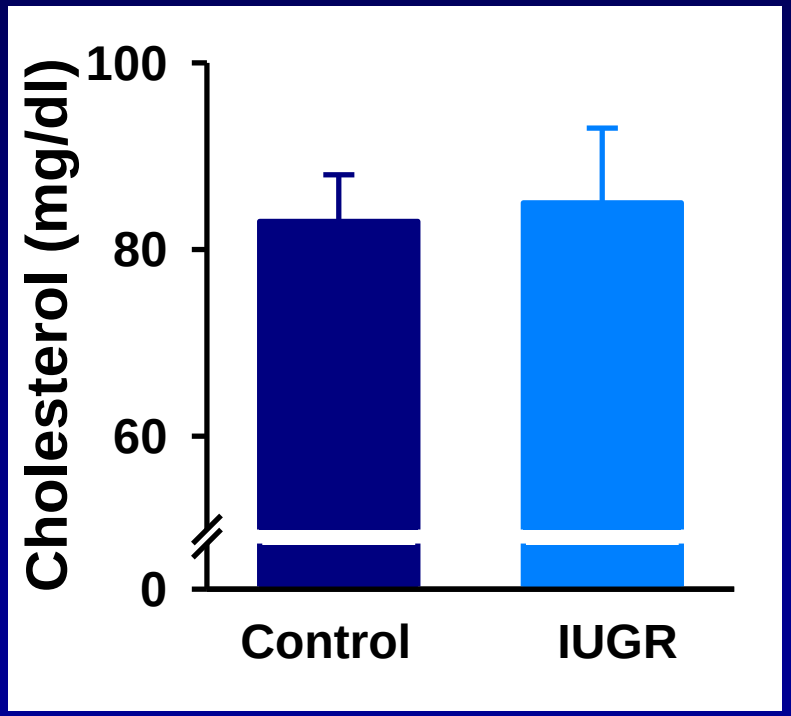
BPA Increases Appetite/Satiety Ratio

Lipid Profile
IUGR Obese Adult Males

Triglyceride



Cholesterol



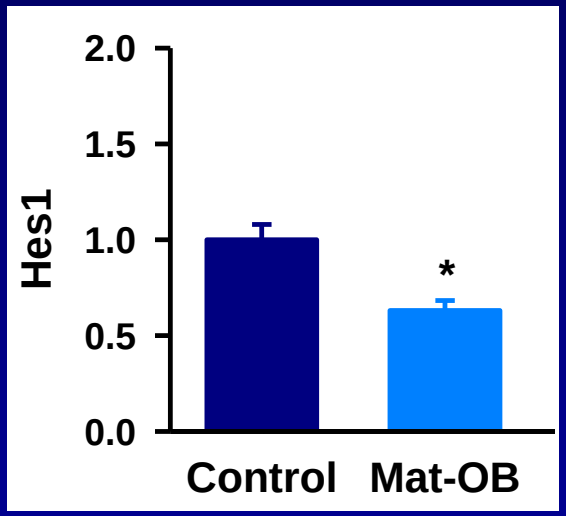
Hypertriglyceridemia

Mean ± SE; * p < 0.001

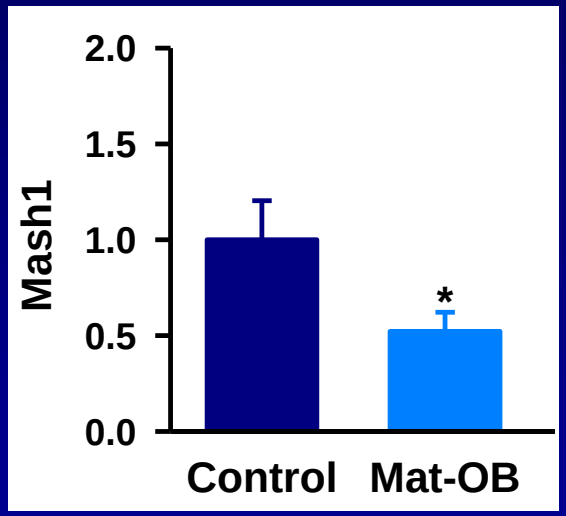
Desai et al, Am J Obstet Gynecol, 2007

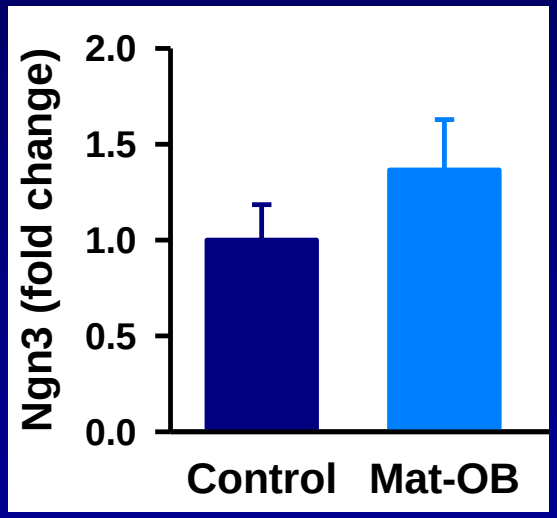
Hypothalamic bHLH Factors
Mat-OB 1 Day Old Newborn

Proliferative



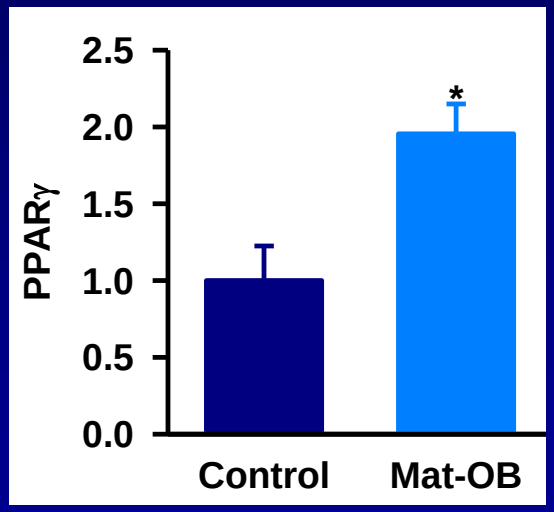
Neurogenic Factors



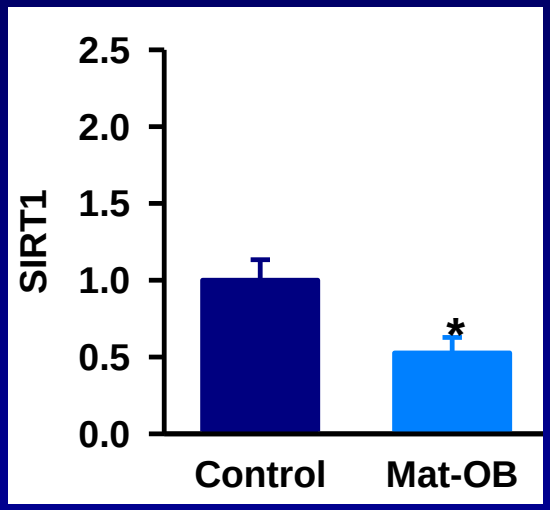


Adipogenic Regulators
Mat-OB 1 Day Newborn

Adipogenic Factor



Repressor



Activator