# Can a Healthy Diet improve Metabolic Outcomes in the Offspring exposed to a Maternal Obesity?

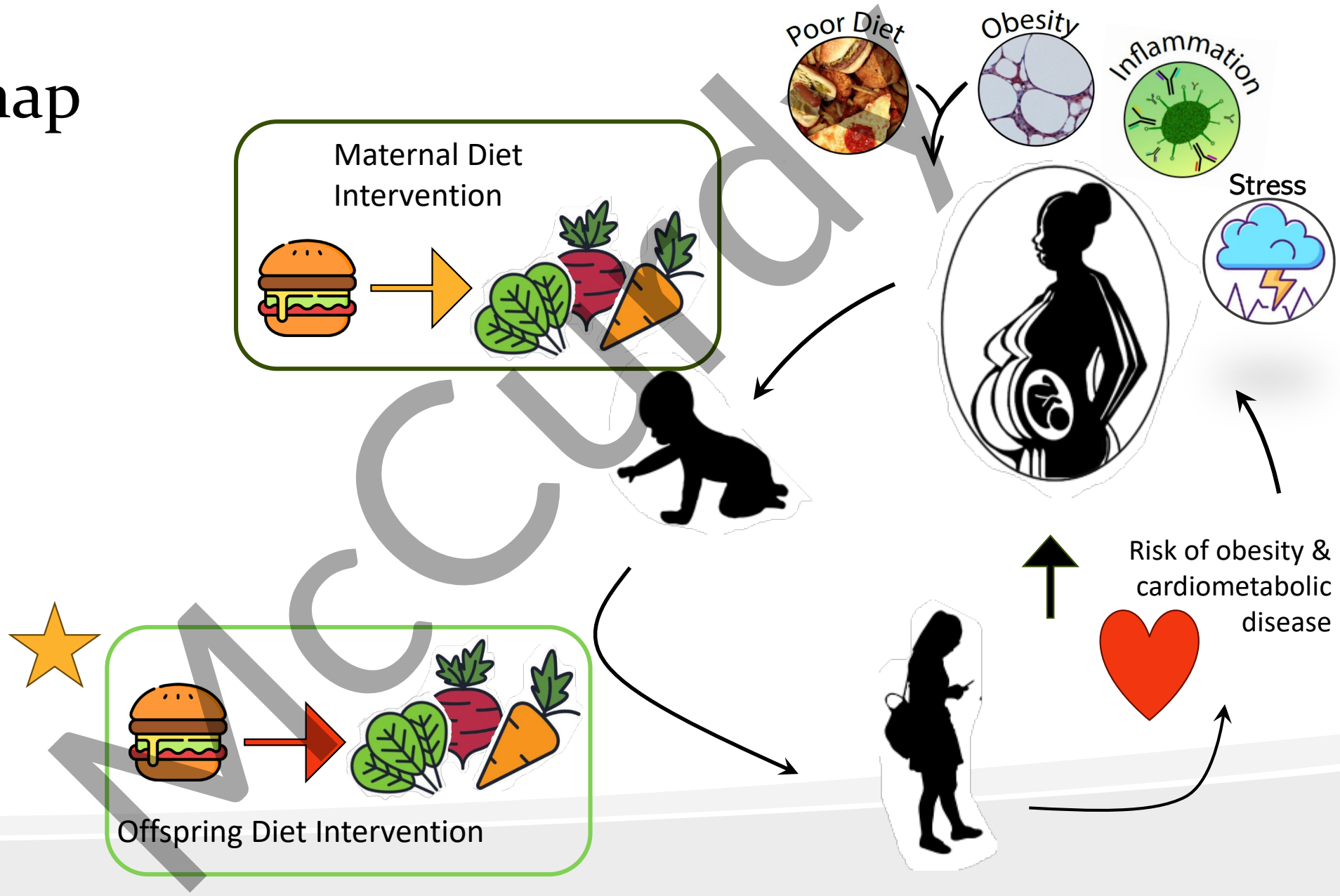
Carrie E. McCurdy, PhD

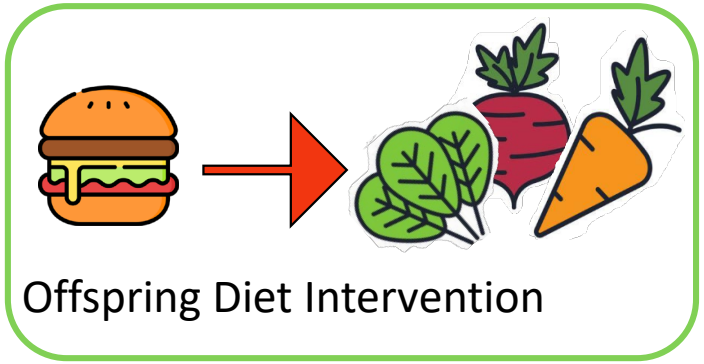
Associate Professor
University of Oregon
Human Physiology
cmccurd5@uoregon.edu

# Learning Objective

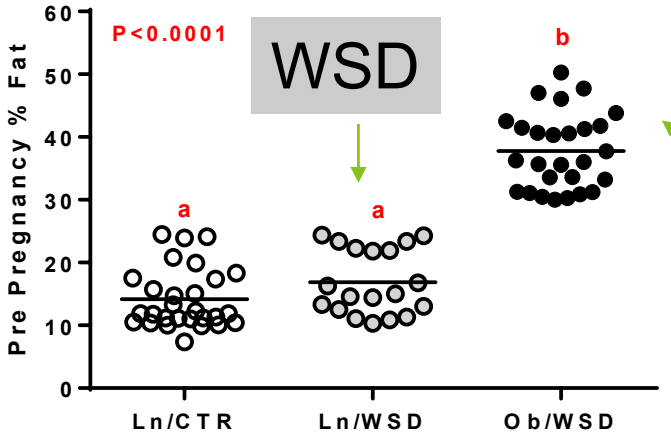
- To evaluate evidence that a healthy diet intervention changes offspring health outcomes
- Focus on findings in the skeletal muscle from a nonhuman primate model

# Roadmap






Can a healthy diet started in early childhood improve offspring outcomes?




Obesity
+WSD
+IR

# Model

## Japanese Macaques

Oregon National Primate Research Center

Diet Group
(2+ years)

Pregnancy

Birth
G165

~7 months

Weaning

CTR

WSD

14 mo

40 mo

**Control (CTR): 13% fat 4% sugars**

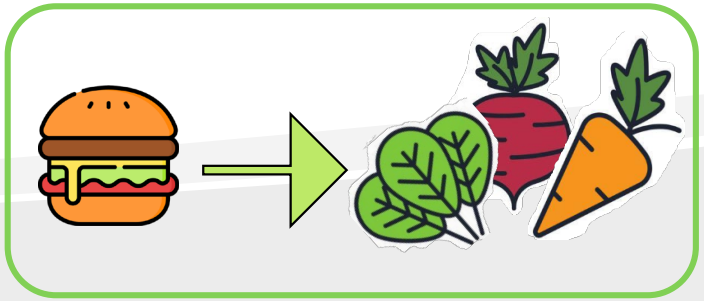
**Lean & Insulin Sensitive** — **Ln/CTR**

**Western Diet (WSD): 35% fat 19% sugars**

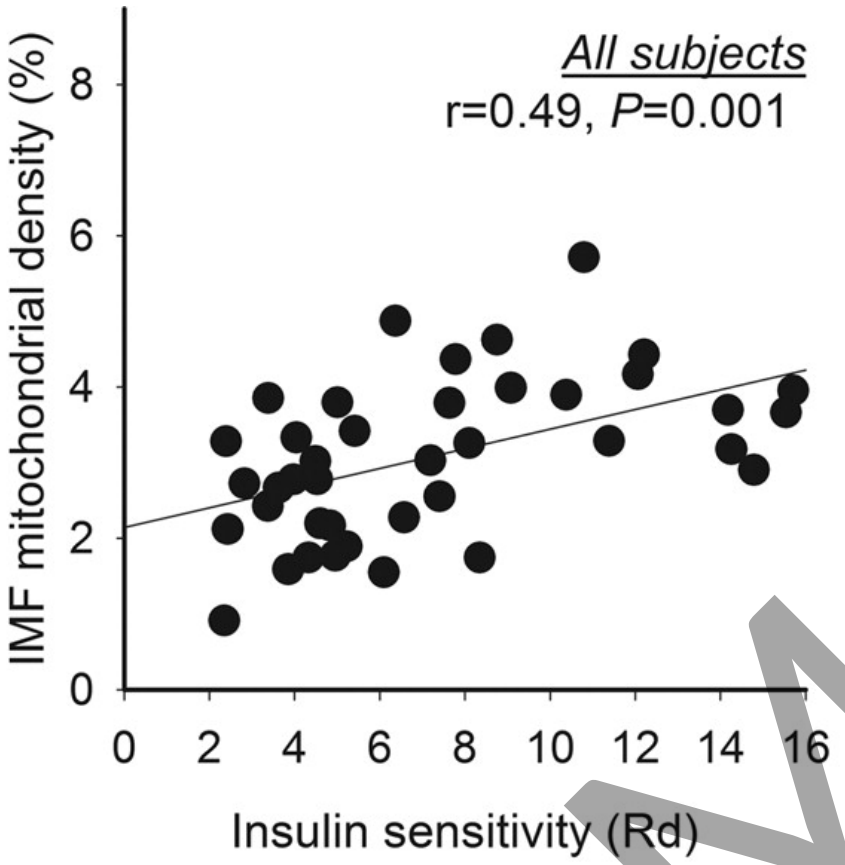
**Lean & Insulin Sensitive** — **Ln/WSD**

**Obese & Insulin Resistant** — **Ob/WSD**

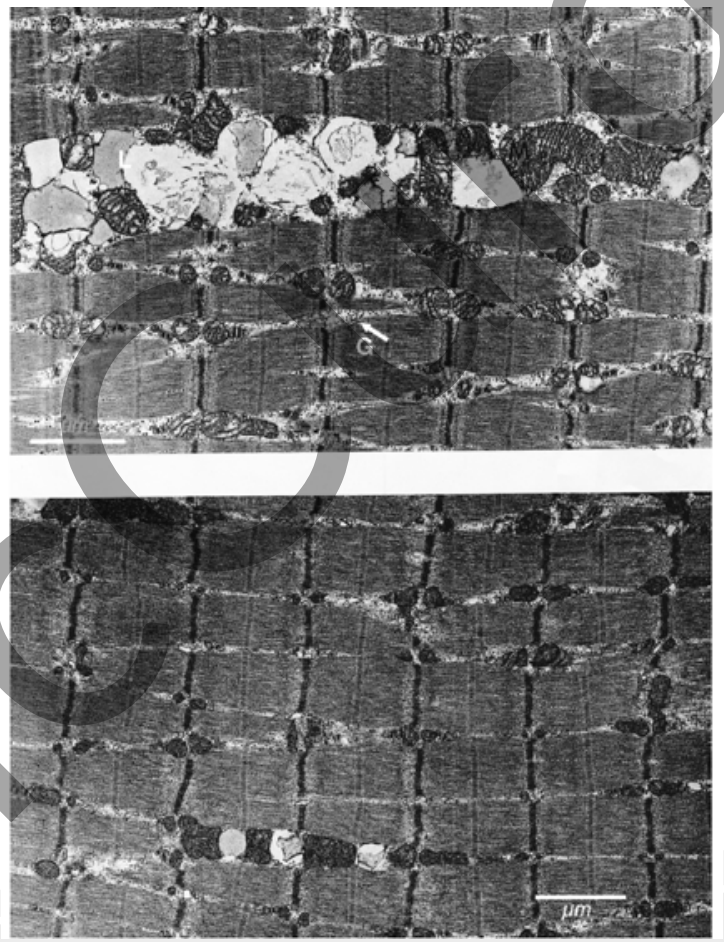
**maternal groups**



# In Skeletal Muscle, mitochondrial health is tightly linked to insulin sensitivity




Obese T2D



Obese Insulin Resistant

**Phentoype of SkM in Obesity**

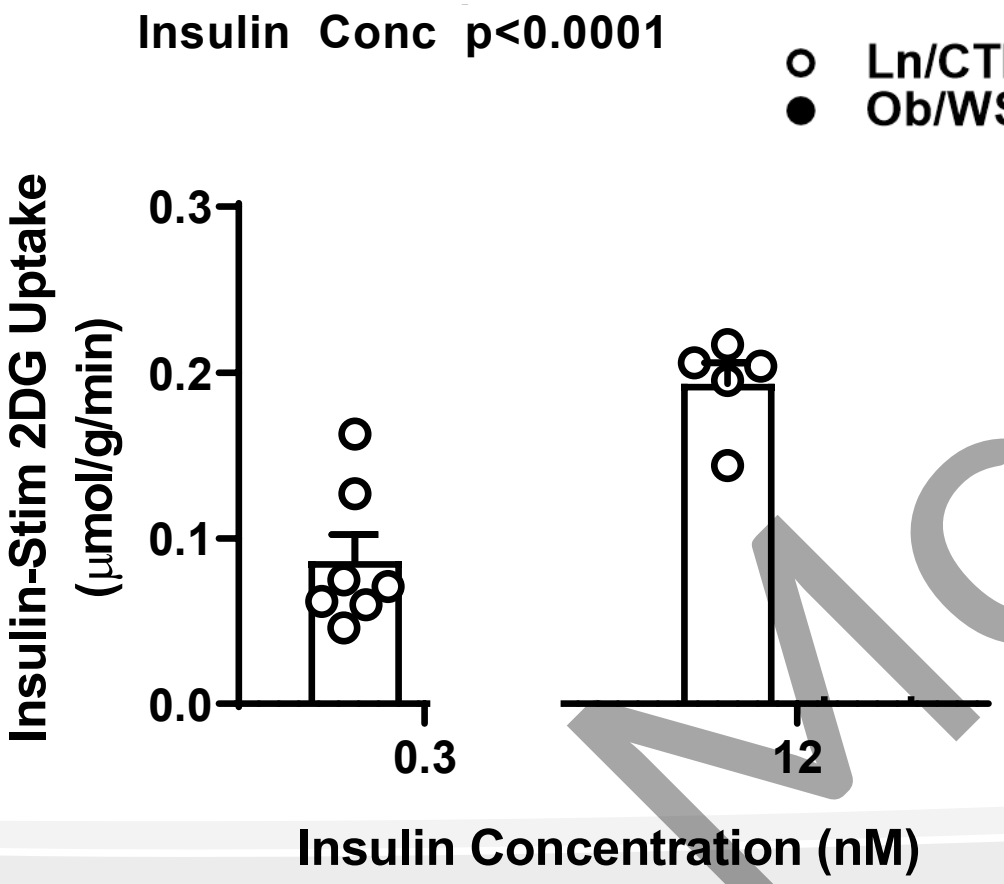
- ↓ Insulin Sensitivity
- ↓ Mito Abundance and/or Function
- ↑ Lipids: TAGs, DAGs, Ceramides, acylCoAs)
- ↑ ROS Production

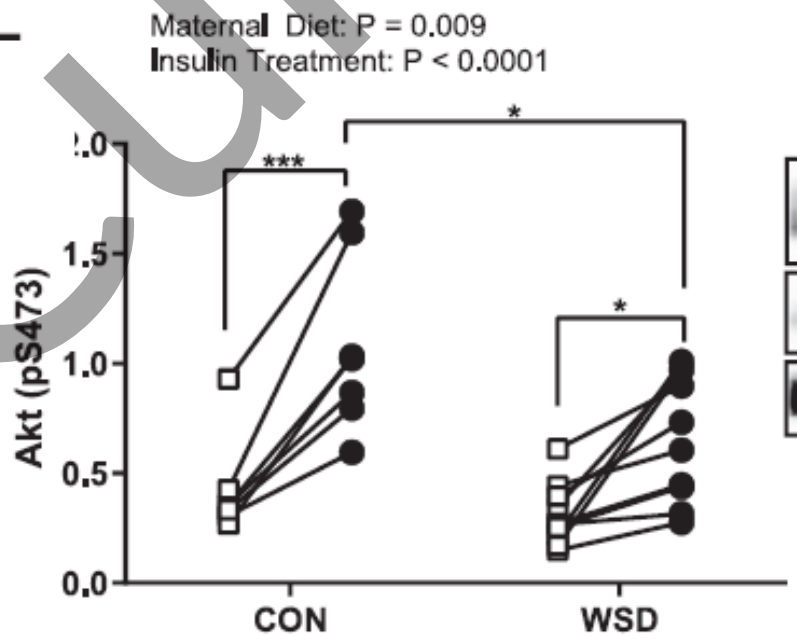


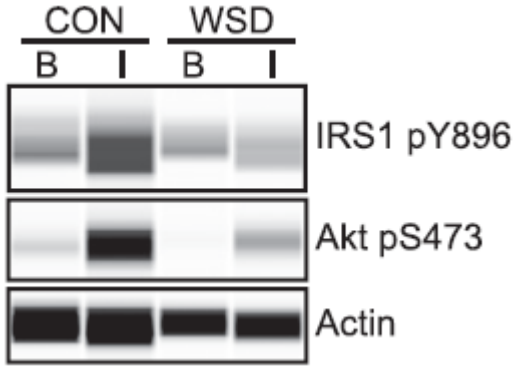
*Chomentowski P et al. JCEM 2011;96:494-503*

# Maternal Obesity reduces I-stim Glucose uptake in Fetal Muscle

Basal and Insulin **Stimulated** [$^3$H] 2-deoxyglucose uptake



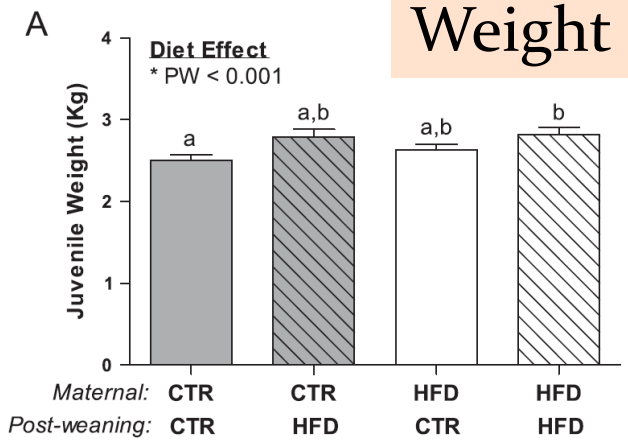



W. Campodonico-Burnett, B. Hetrick et al. (2020) Diabetes. 69:1389-1400

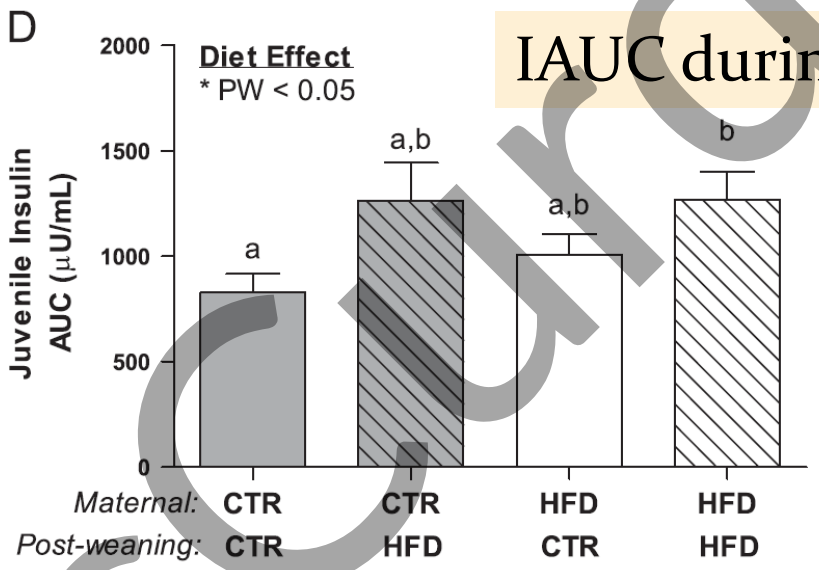
# Impact of Healthy Postweaning Diet?

Juvenile Offspring
14 mo

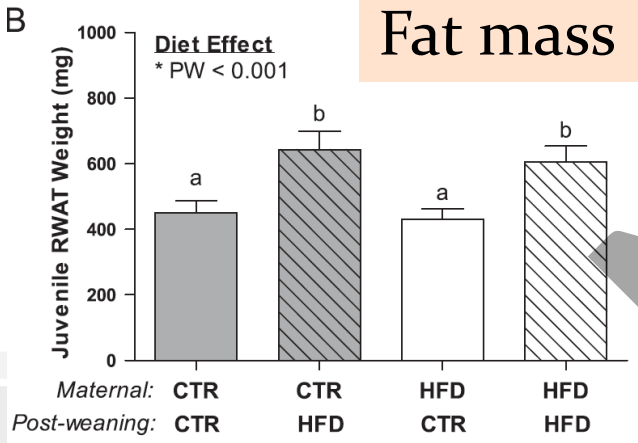
## Weight




## IAUC during iv GTT



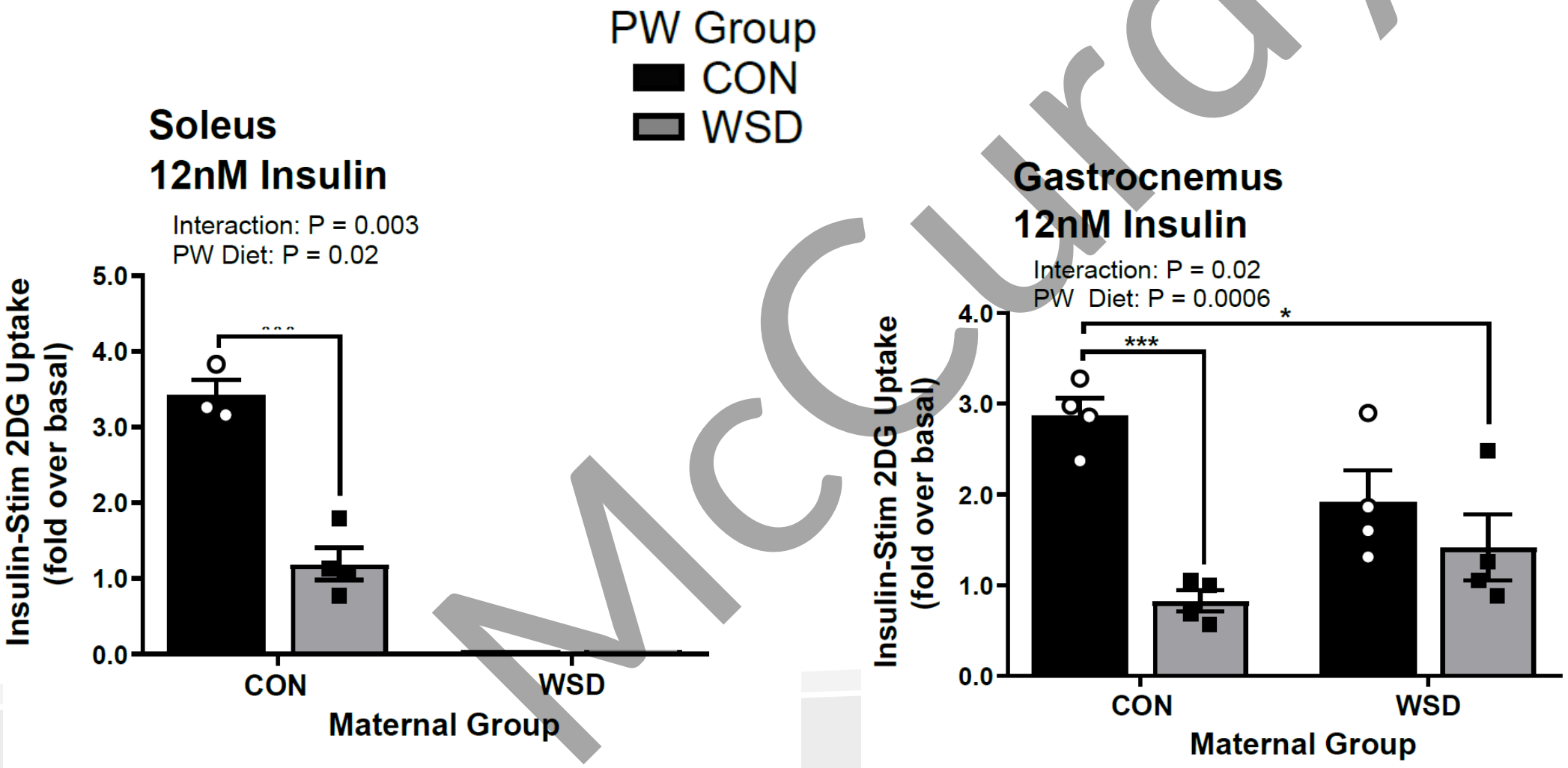

## Fat mass




No difference by **Maternal diet** on offspring adiposity or measures of systemic insulin resistance

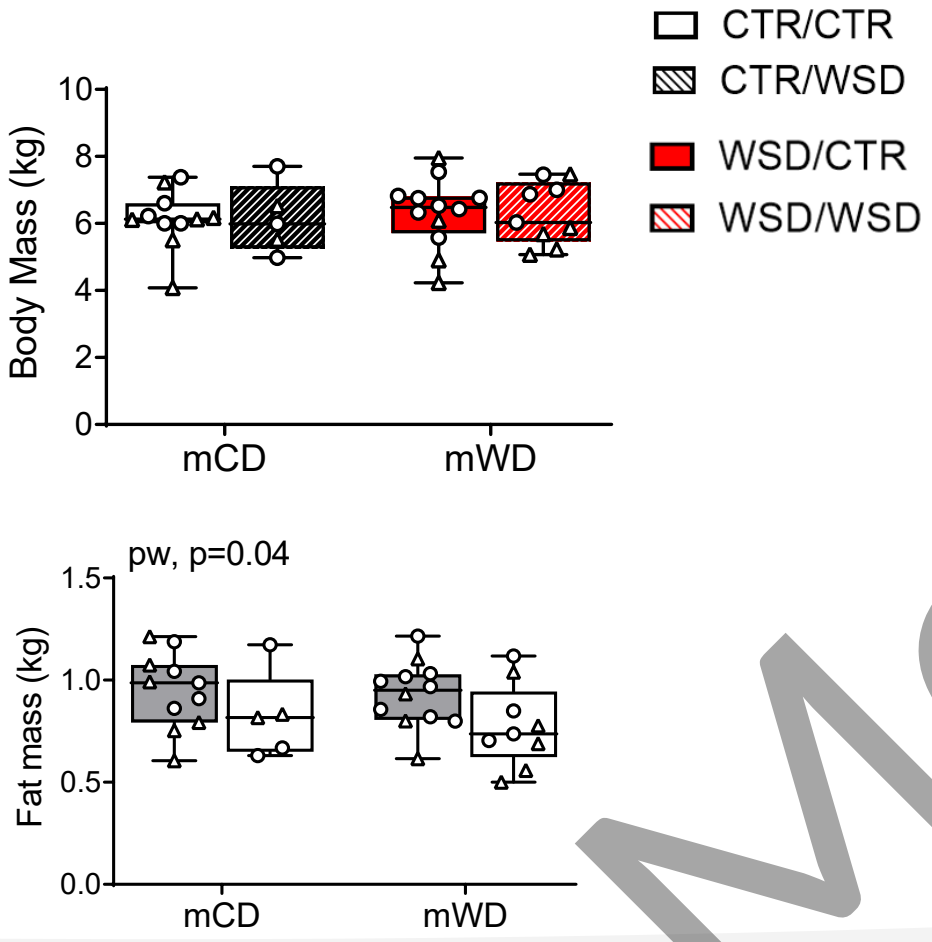
Juvenile Offspring
14 mo

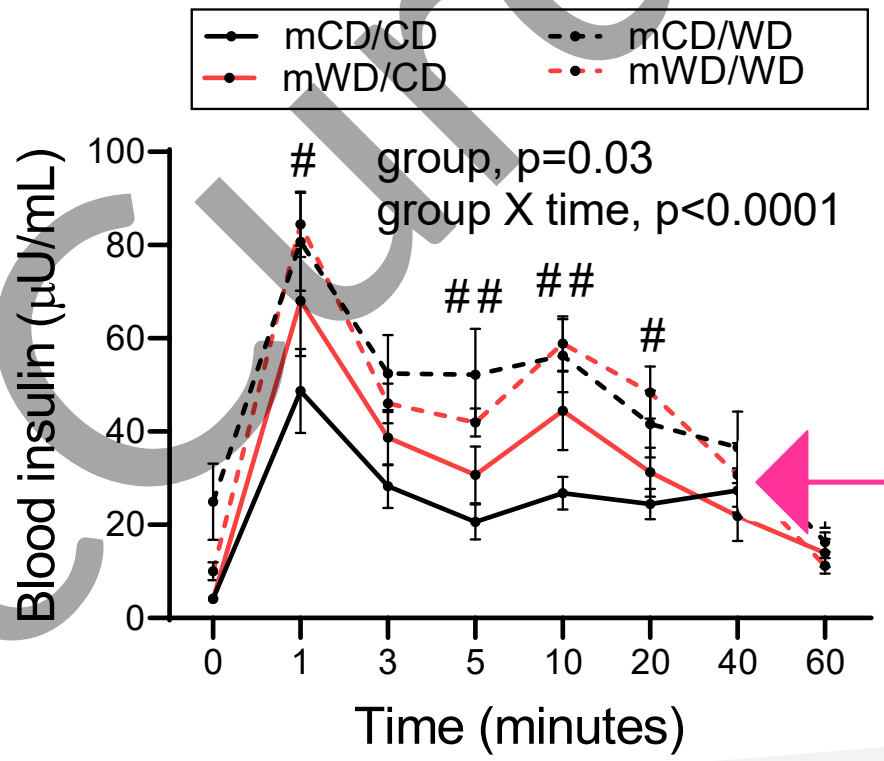
# Impact of Healthy Postweaning Diet?



# Impact of Healthy Postweaning Diet?

Adolescent Offspring
40 mo



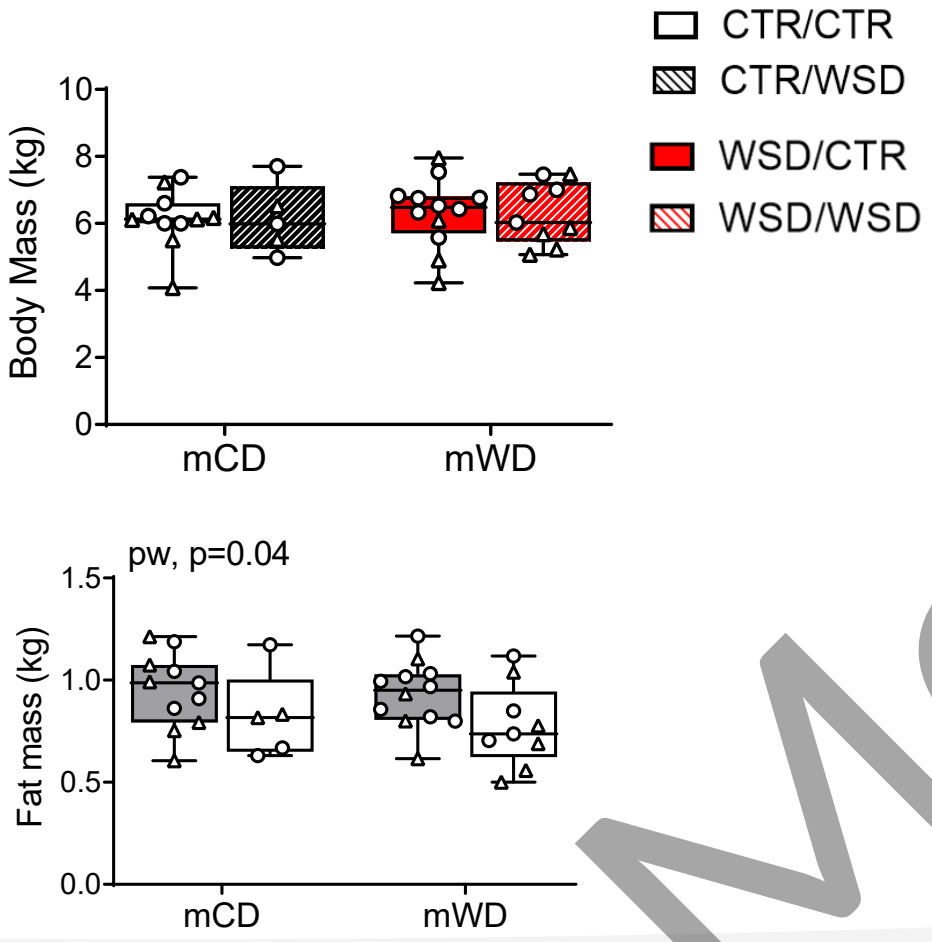

Healthy Diet Intervention

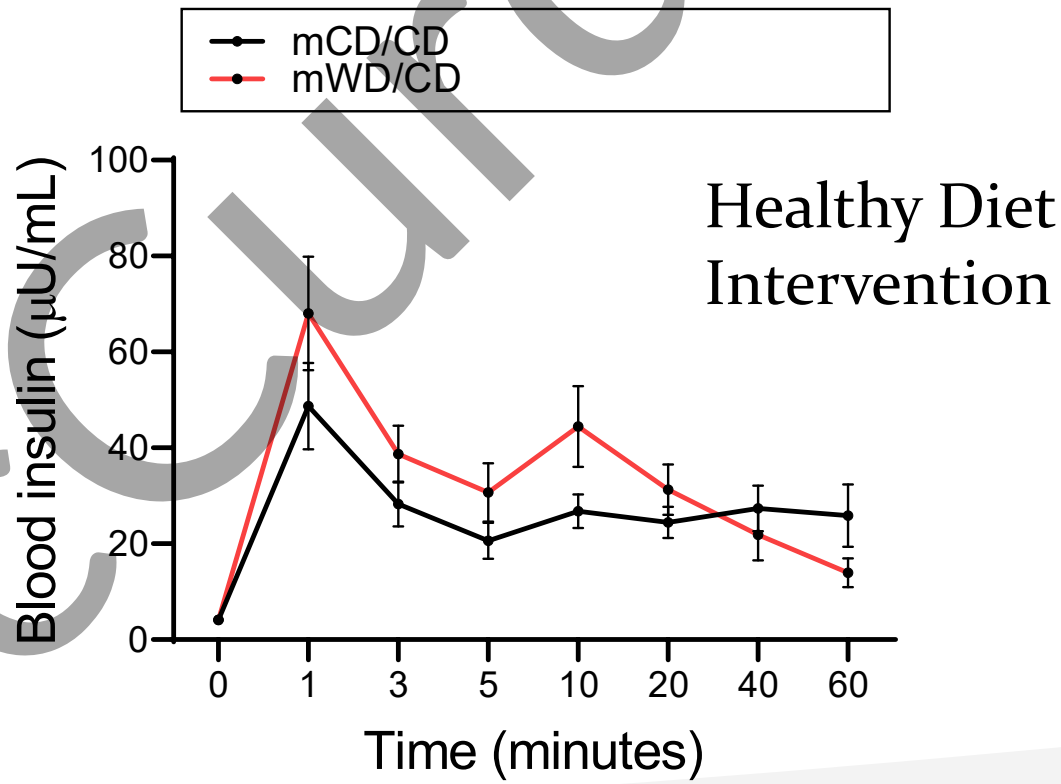
Insulin AUC

*K. Greyslak, Unpublished*

# Impact of Healthy Postweaning Diet?

Adolescent Offspring
40 mo




Healthy Diet Intervention

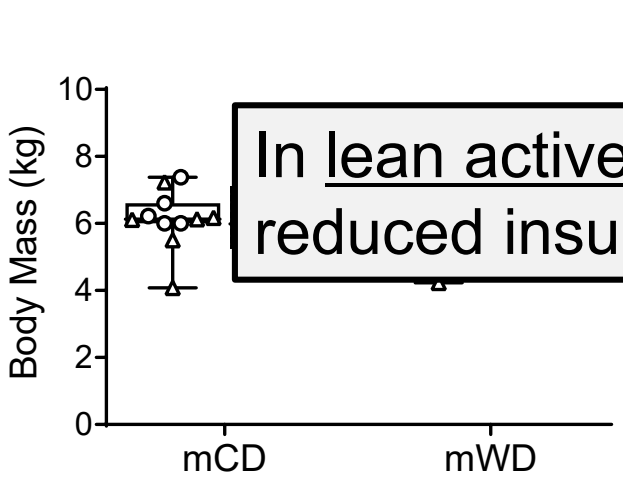
Insulin AUC

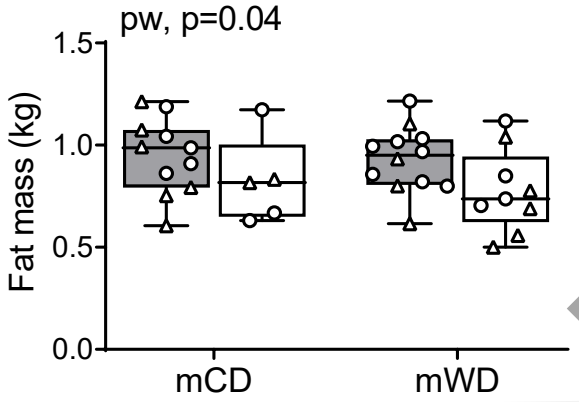
*K. Greyslak, Unpublished*

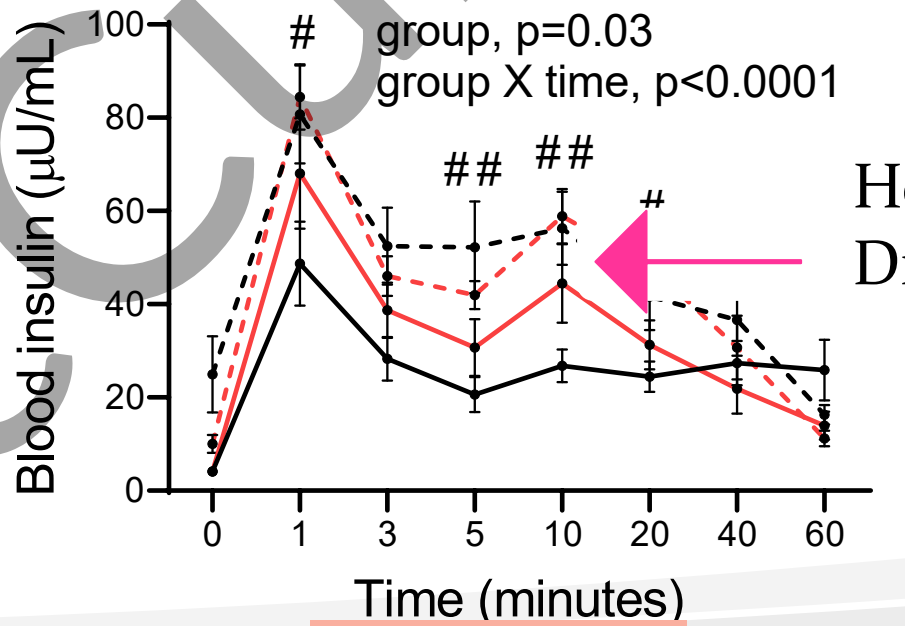
Adolescent Offspring
40 mo

# Impact of Healthy Postweaning Diet?

In lean active adolescent, **maternal WD** or postweaning WD reduced insulin sensitivity



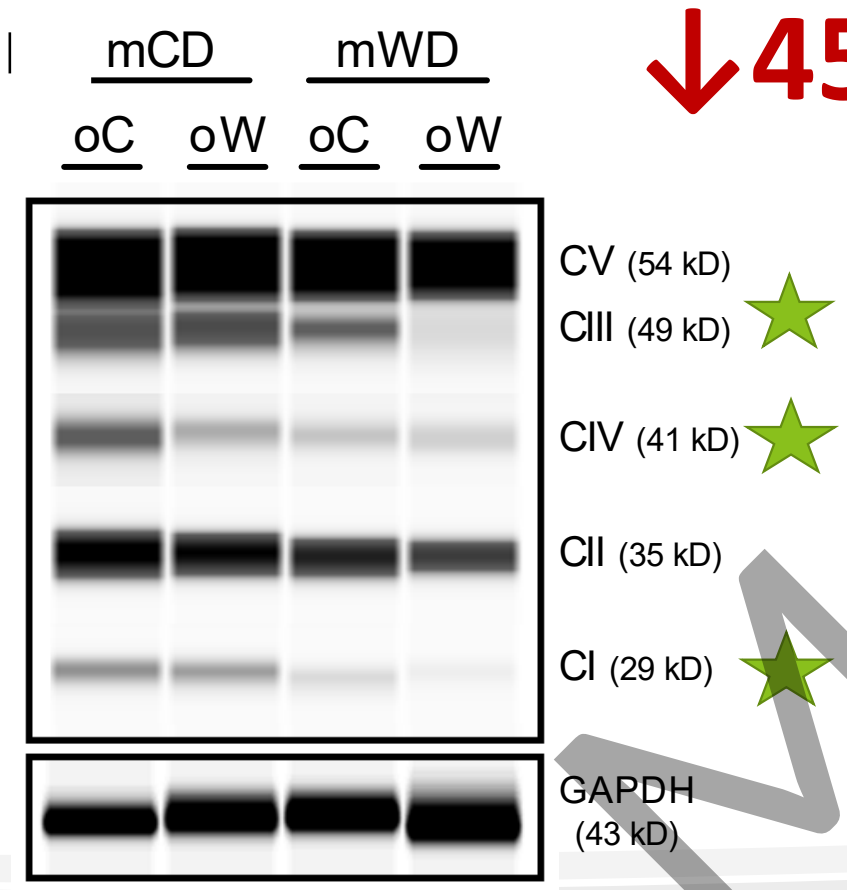

Healthy
Diet Intervention

Insulin AUC

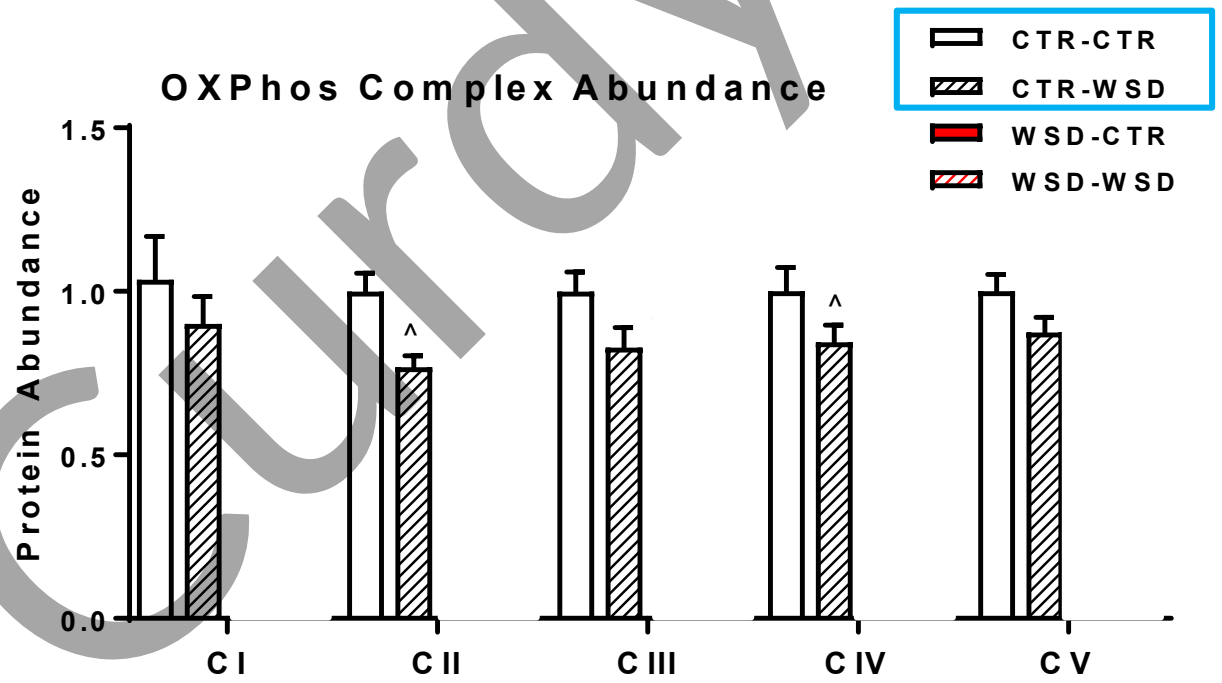
*K. Greyslak, Unpublished*

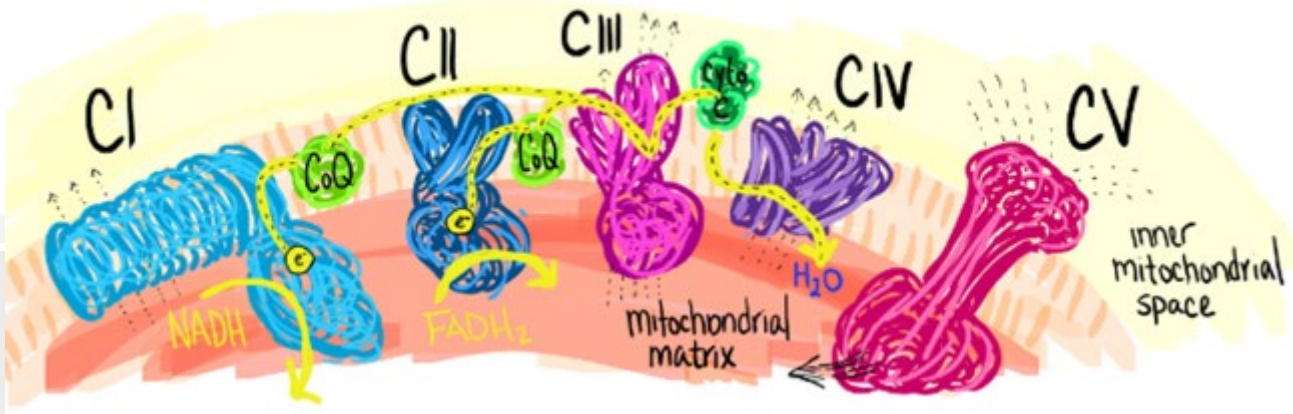
# What about Skeletal Muscle Mito?

Adolescent Offspring
40 mo




↓45%



Adolescent Offspring
40 mo

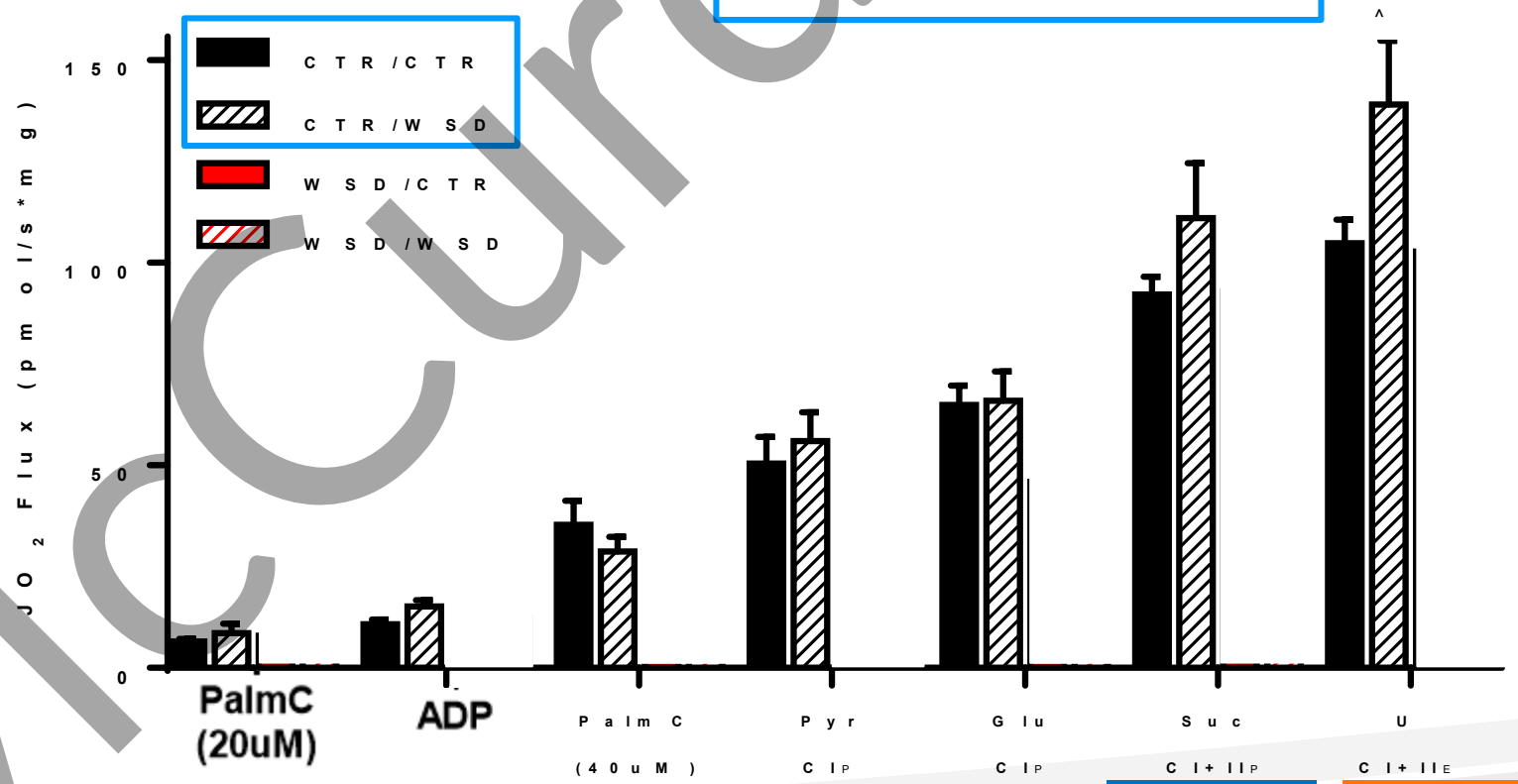
# Oxidative Metabolism Muscle

**Offspring from maternal CTR Diet**

Permeabilized Muscle Fiber Bundles (PmFB)

Gastroc

OxPHOS with Lipid




LEAK | ETF+CI | CI+II | ETS CAPACITY

OXPHOS CAPACITY

*Unpublished data* p<0.05 * by mDiet, same pwDiet; ^ by pwDiet, same mDiet

# Oxidative Metabolism In Muscle

Adolescent Offspring
40 mo

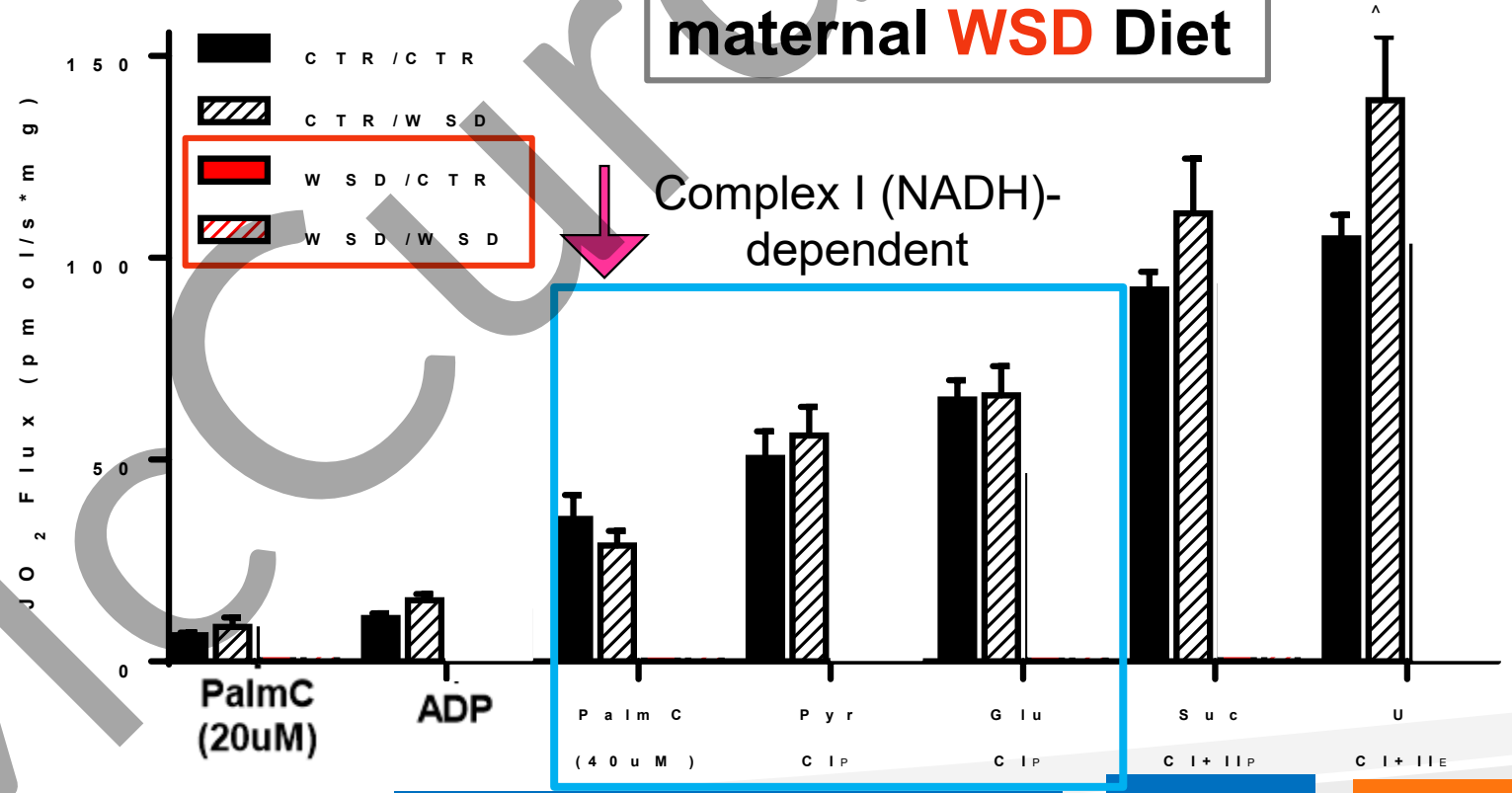
Permeabilized Muscle Fiber Bundles (PmFB)

- Gastroc
- Soleus

OxPHOS with Lipid

OxPHOS with Pyruvate

**Offspring from maternal WSD Diet**




*Unpublished data* p<0.05 * by mDiet, same pwDiet; ^ by pwDiet, same mDiet

# LIPID OXIDATION IN SOLEUS

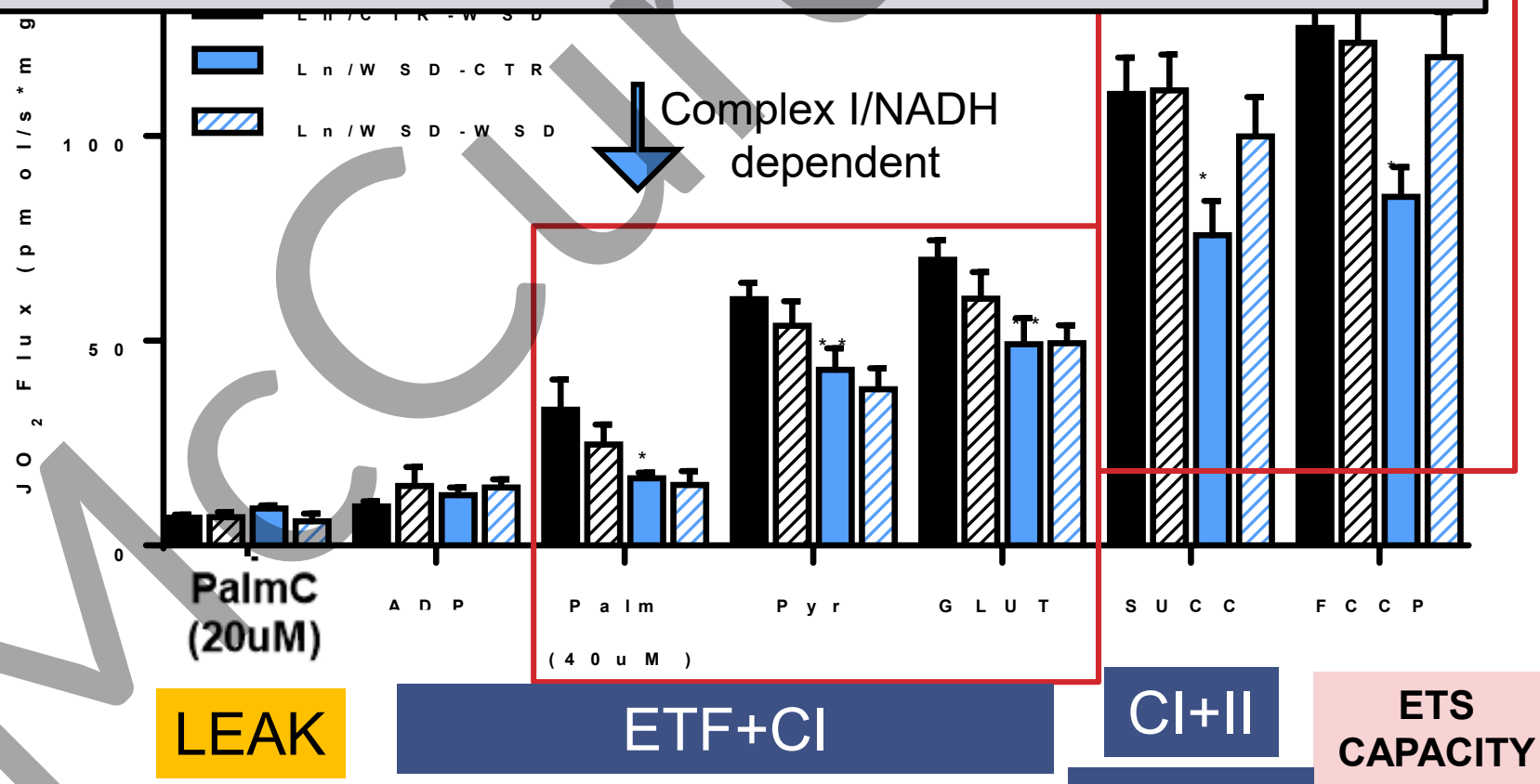
Adolescent Offspring
40 mo

Prior exposure to a **maternal WD** suppressed Oxidative Metabolism even when offspring were **switched to a healthy diet** in offspring

Perme
Fiber B

- Gastroc
- Soleus

OxPHOS with Lipid

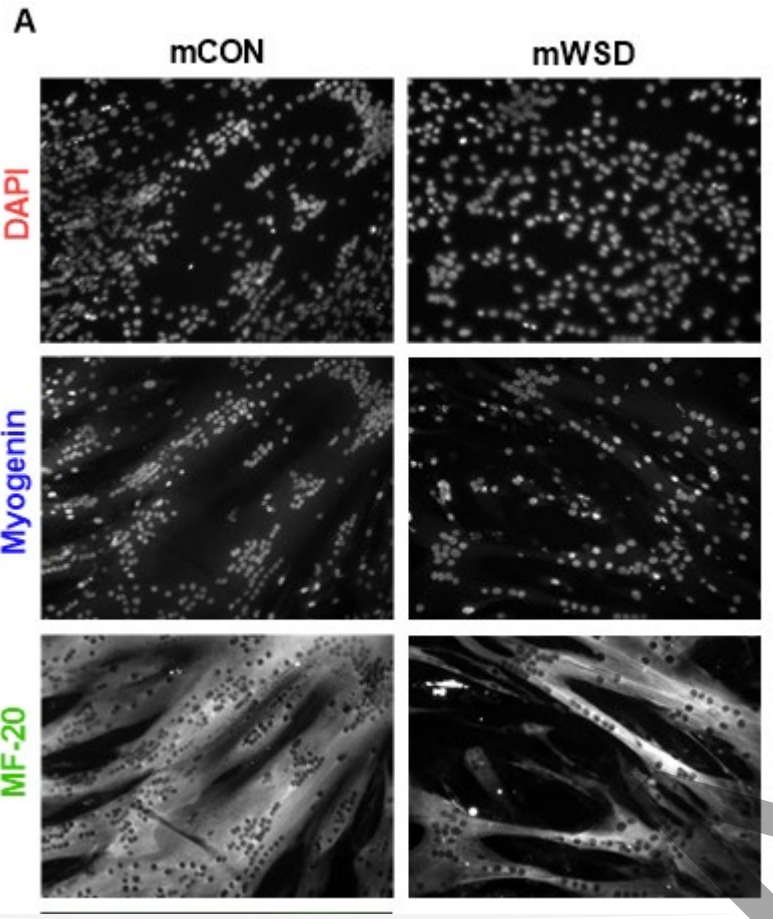



*Greyslak, Unpublished data*

# Metabolic and growth defects persist in primary myotube

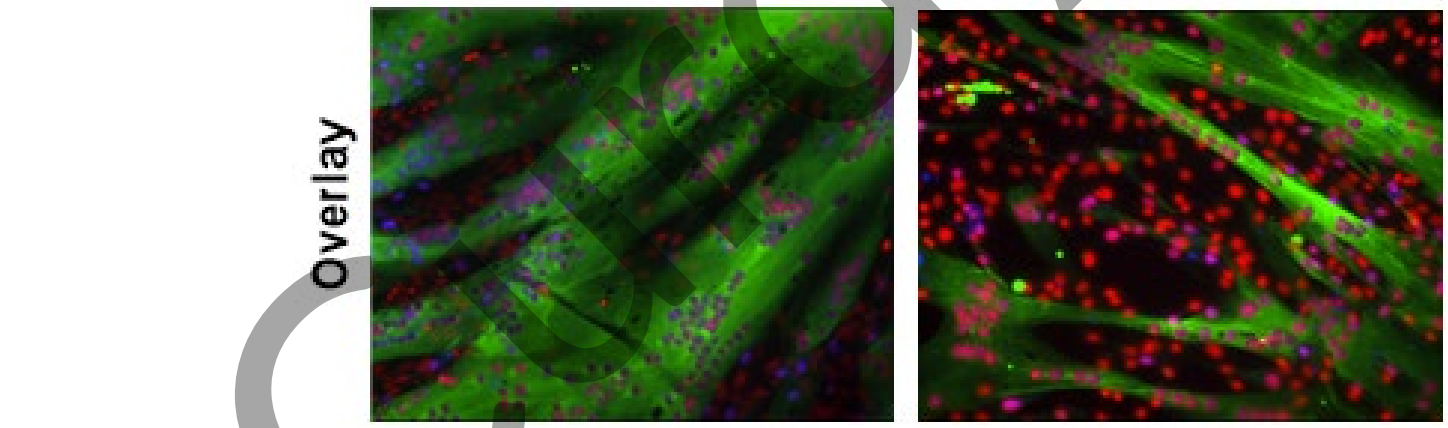
Adolescent Offspring

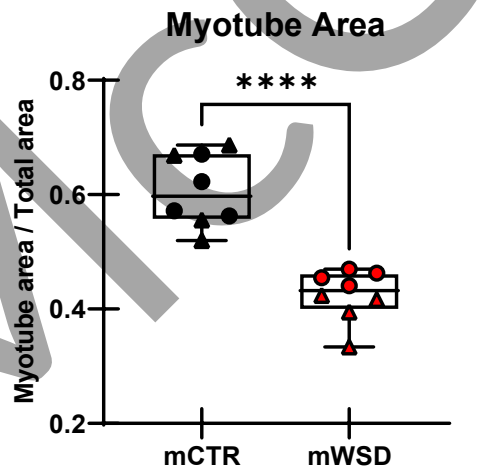
5d Post Differentiation

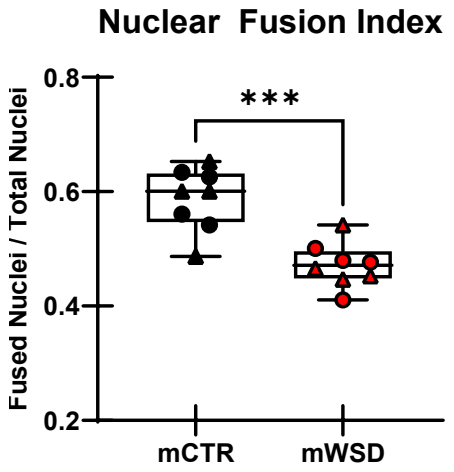


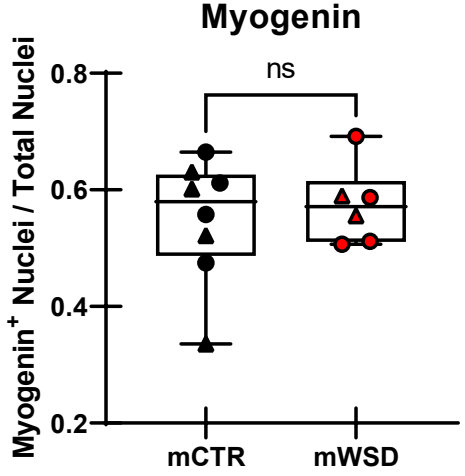

mCON/CON mWSD/CON

Overlay





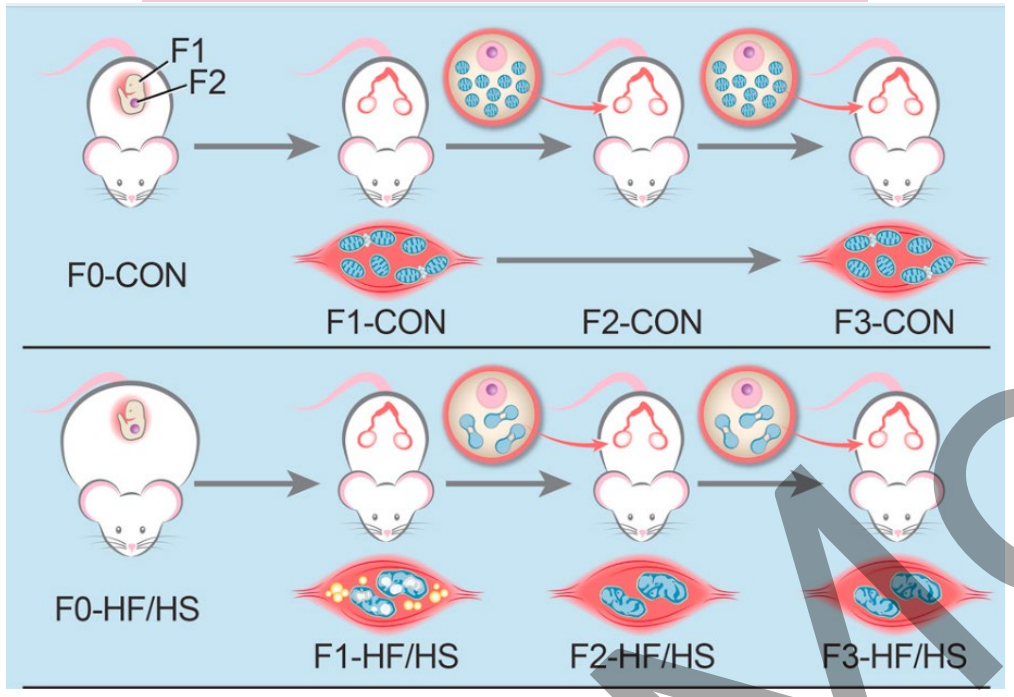


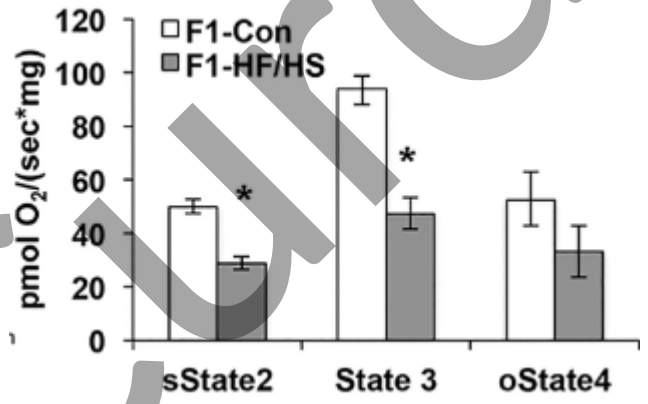

*D. Foote, Unpublished*

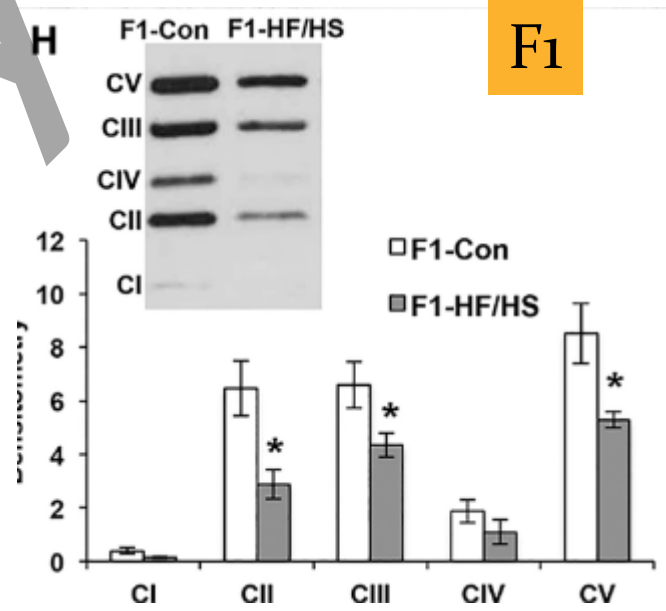
# Multigenerational Impact of Maternal Diet on Muscle function

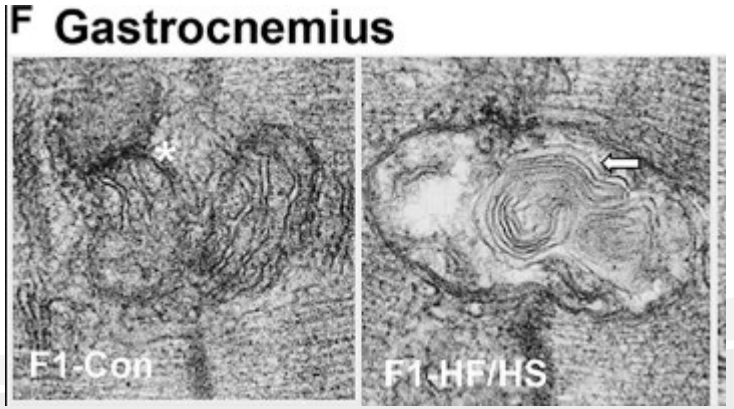
F1

Offspring → control diet






Jessica L. Saben, .., **Kelle H. Moley**. Maternal Metabolic Syndrome Programs Mitochondrial Dysfunction via Germline Changes across Three Generations. **Cell Reports**, 16, Issue 1, 2016.

# A healthy postweaning diet intervention is not sufficient to reverse the effects of a poor-quality maternal diet +/- obesity

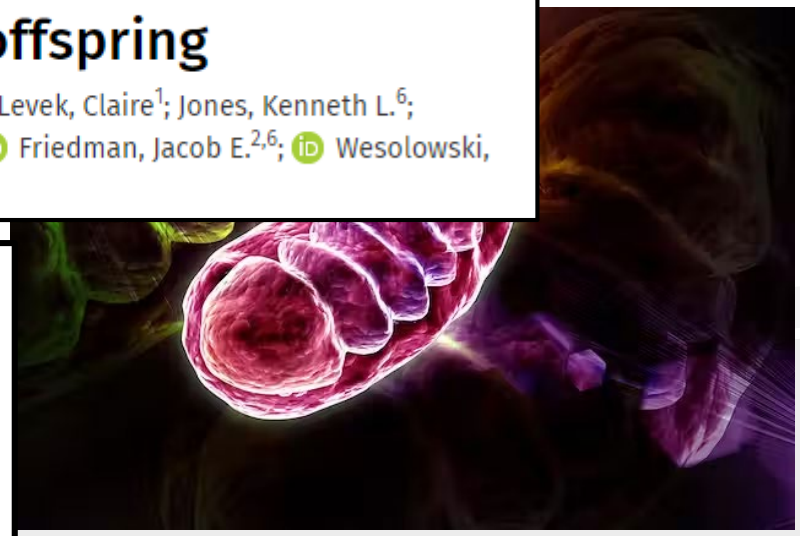
Cell Reports

**Maternal diet alters long-term innate immune cell memory in fetal and juvenile hematopoietic stem and progenitor cells in nonhuman primate offspring**

Skeletal muscle mito
Insulin sensitivity

**Maternal Western diet is associated with distinct preclinical pediatric NAFLD phenotypes in juvenile nonhuman primate offspring**

Nash, Michael J.[1]; Dobrinskikh, Evgenia[1]; Janssen, Rachel C.[2]; Lovell, Mark A.[3,4]; Schady, Deborah A.[5]; Levek, Claire[1]; Jones, Kenneth L.[6]; D'Alessandro, Angelo[7]; Kievit, Paul[8]; Aagaard, Kjersti M.[9,10,11]; McCurdy, Carrie E.[12]; Gannon, Maureen[13]; Friedman, Jacob E.[2,6]; Wesolowski, Stephanie R.[1]

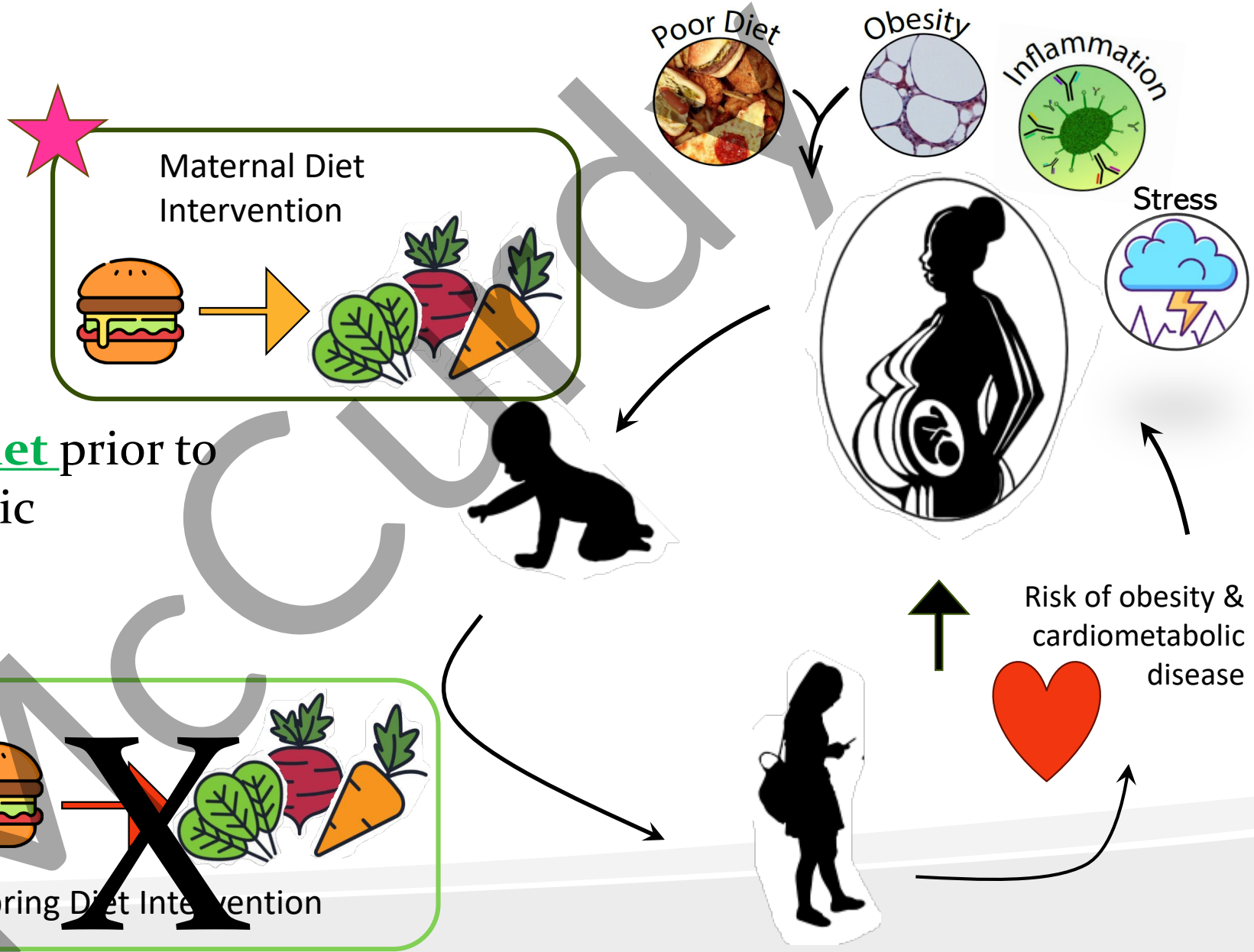


Mol Metab. 2019 Jul;25:73-82. doi: 10.1016/j.molmet.2019.03.010. Epub 2019 Apr 12.

**Maternal Western-style diet affects offspring islet composition and function in a non-human primate model of maternal over-nutrition**

# Roadmap

Can switching to **healthy diet** prior to pregnancy improve metabolic outcomes in the offspring?



# Experimental Model

Prior Years (4-9)

Study Year

Diet switch

3mo

Breeding Period

C-section G130/165

**Western-Style Diet**
**35% fat**
**19% sugars**

**Control Diet**

**Western-Style Diet**

**Western-Style Diet**

**Control (CTR):**
**13% fat**
**4% sugars**

**Control Diet**

Chronic Diet (~9yrs)

Fetal Offspring

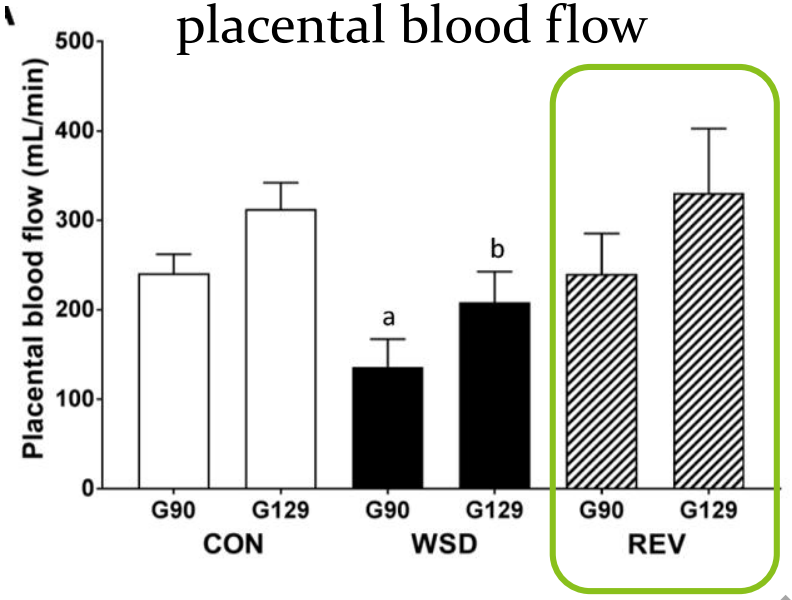
**Ob/DR**

**Ob/WSD**

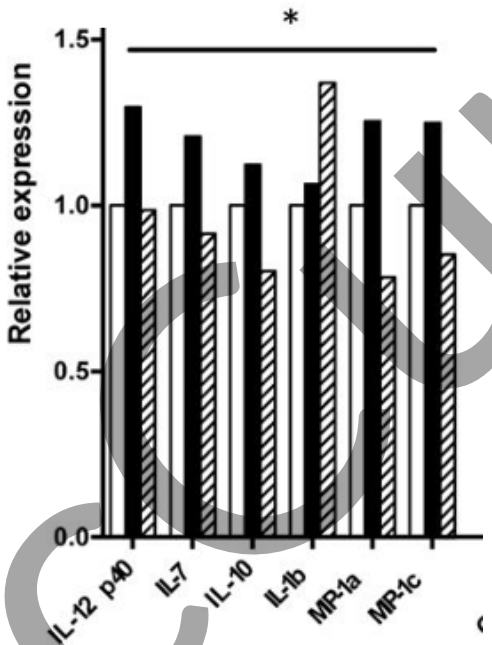
**Ln/CTR**

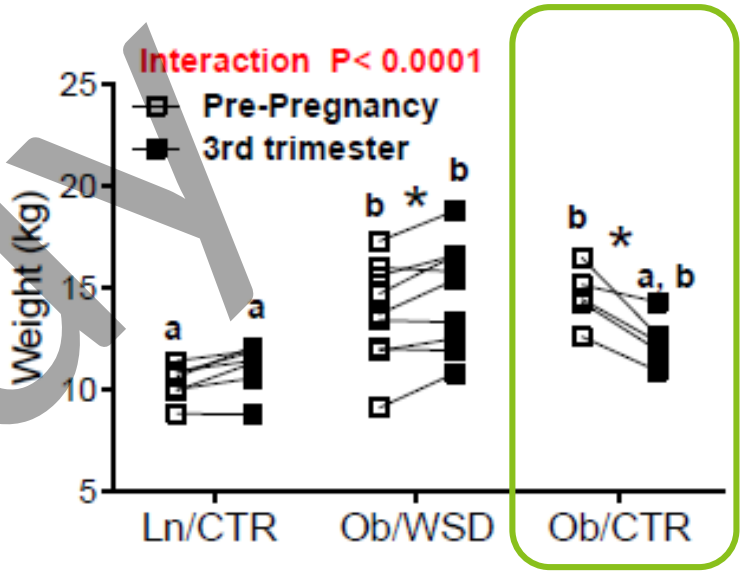
# Maternal- Placental Phenotype

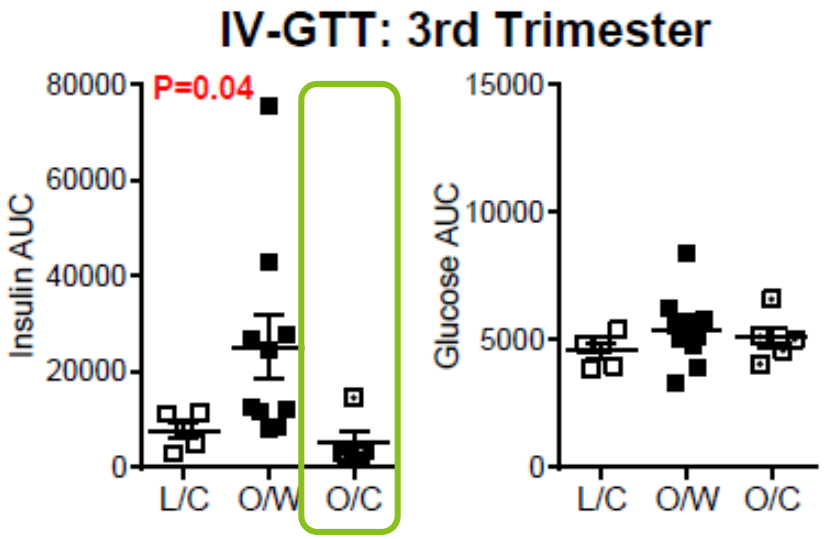
placental blood flow




placental Inflammation



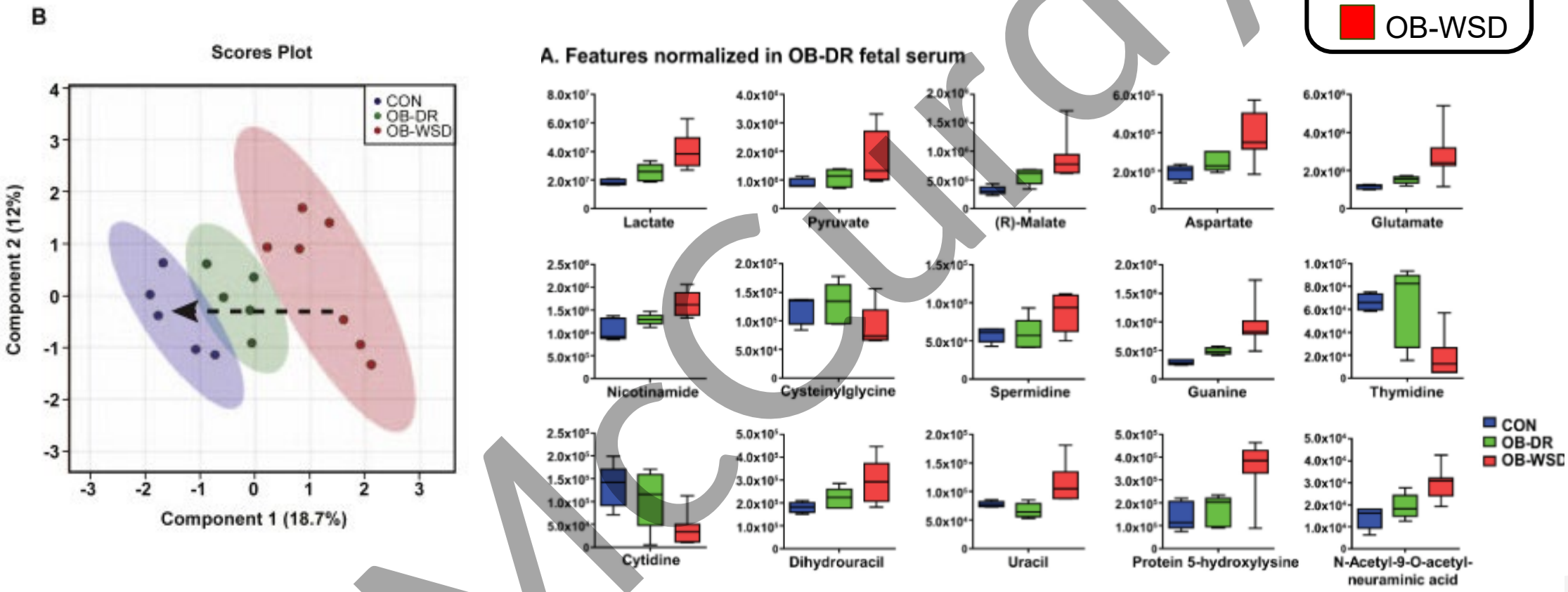

Healthy diet switch prior to pregnancy improves maternal-placental metabolic profile



JA Salati, V Roberts…A Frias (2019) Int J Obes 43:906

CE McCurdy (2016) JCI Insight 1:e86612

# Some Fetal Serum metabolites Improve

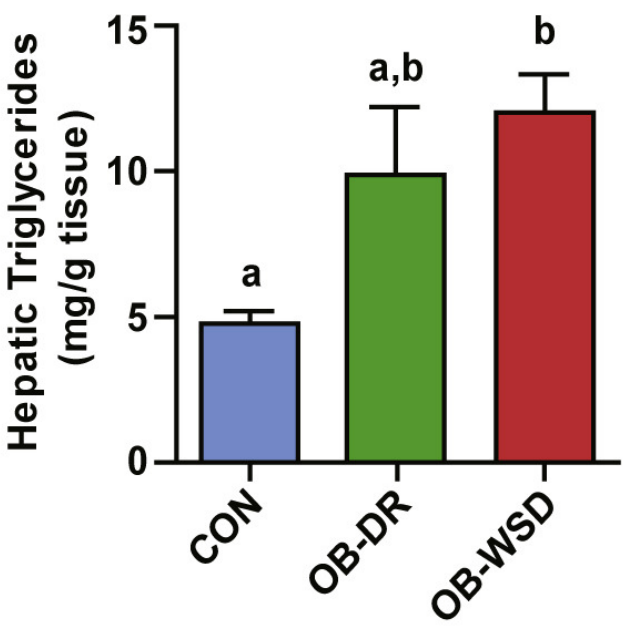


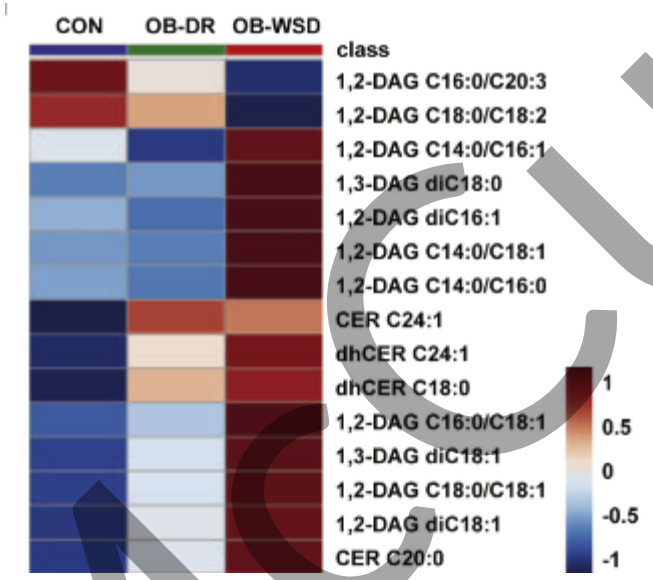



SR Wesolowski et al (2018) Mol Metab 18: 25

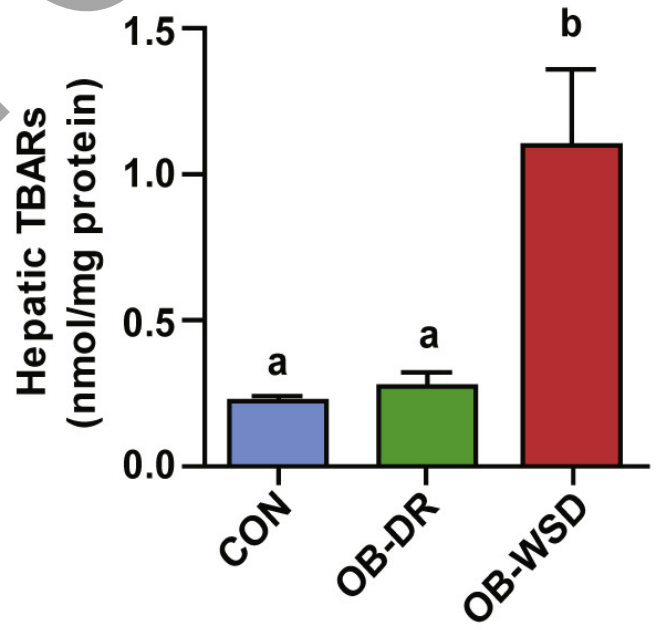
# Healthy Maternal Diet intervention improves some Metabolic Endpoints in the Fetal Liver

## Hepatic lipids



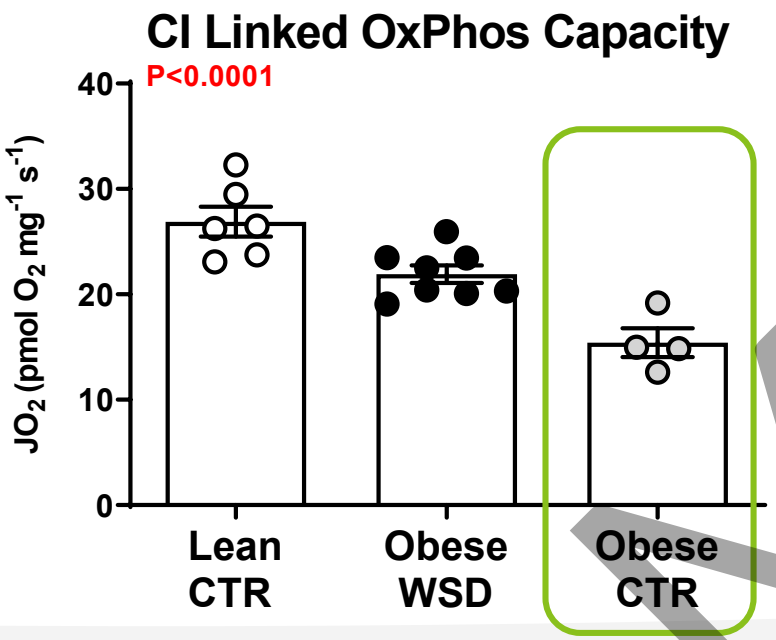

## ↓ Oxidative Damage



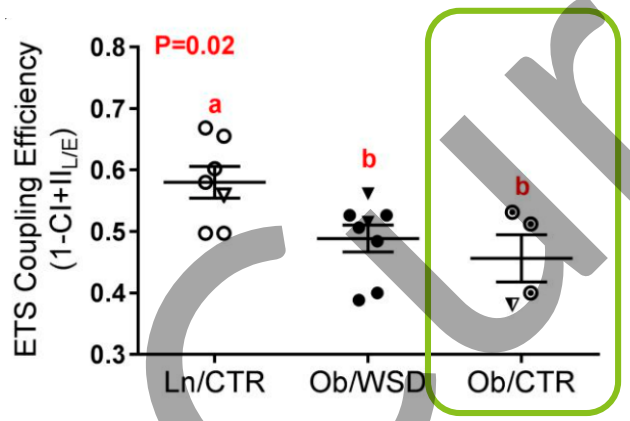

SR Wesolowski et al (2018) Mol Metab 18: 25

# Metabolic defects persist in fetal skeletal muscle

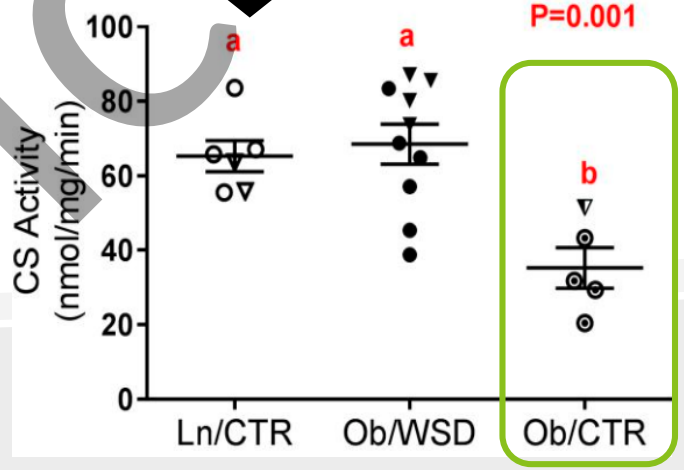
Fetal
muscle fibers



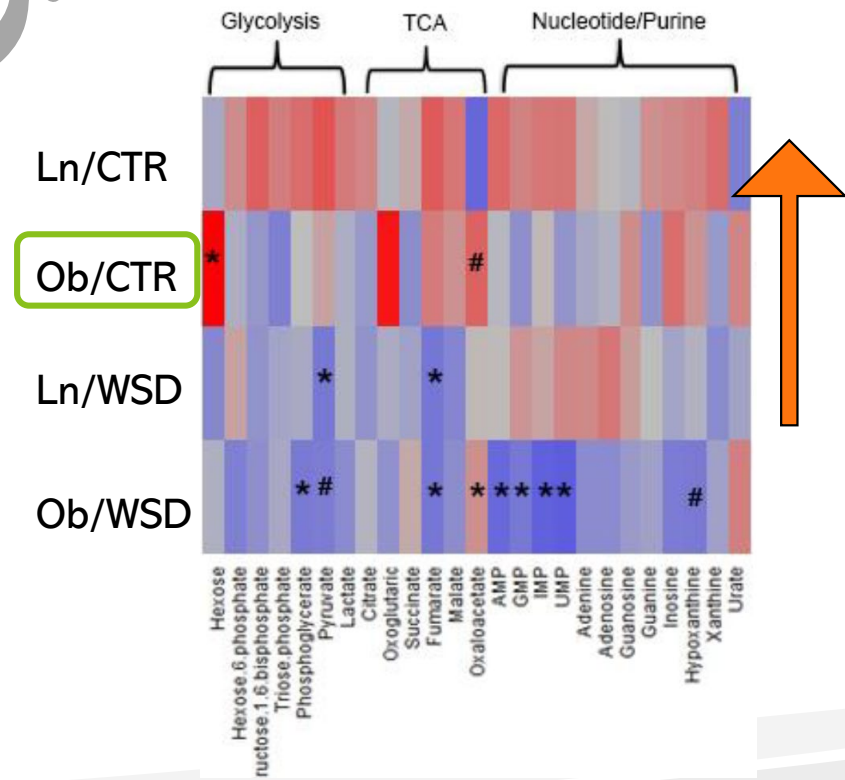

Efficiency




Mito Content



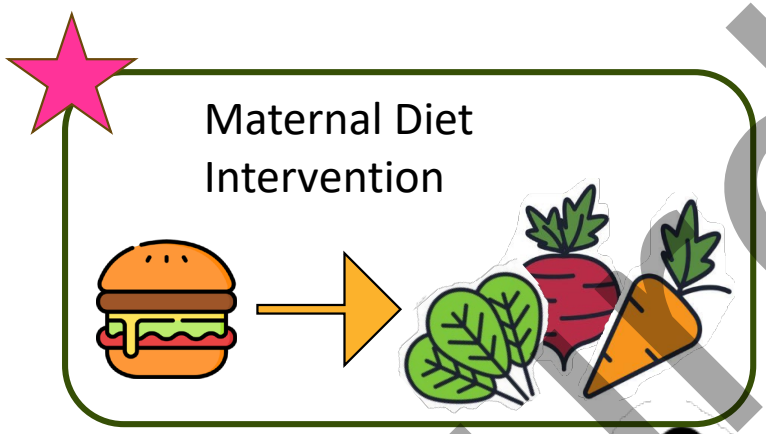

Metabolites

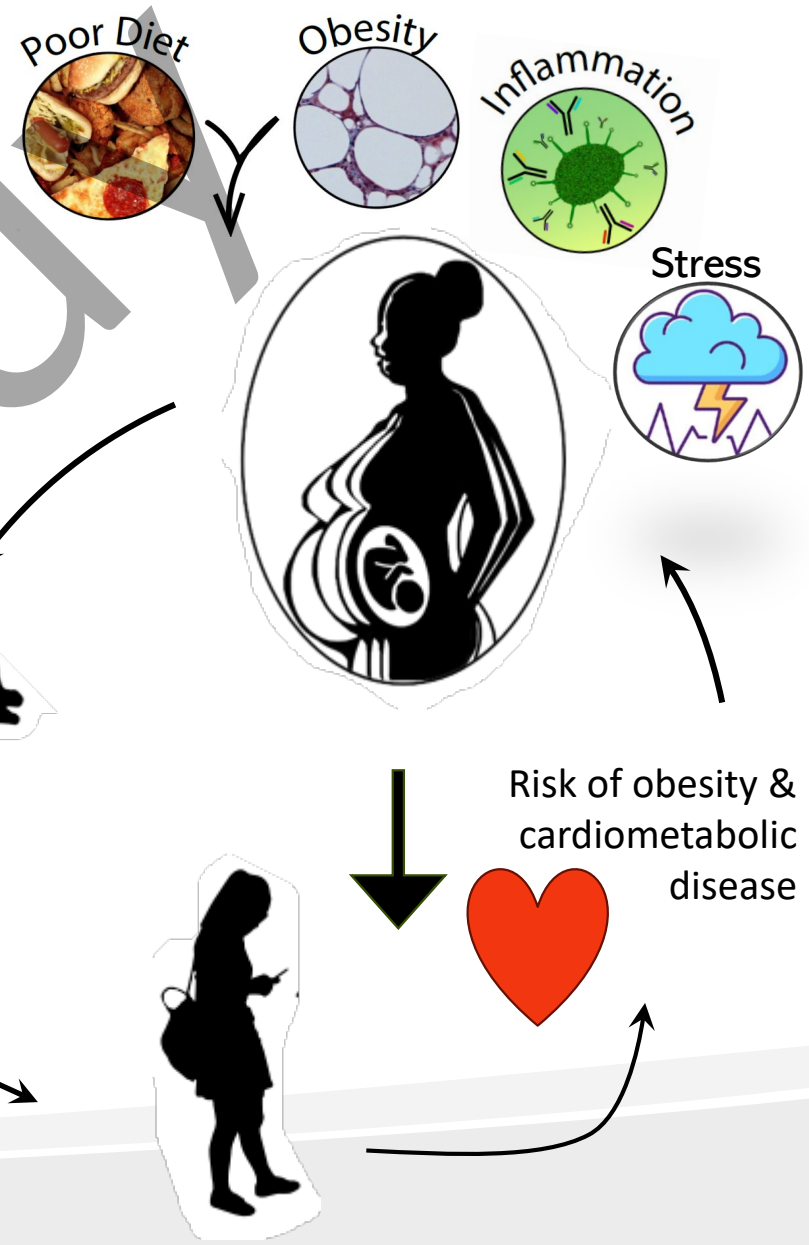





McCurdy, et al. (2016) JCI Insight

# Summary




Switching to **healthy diet prior to pregnancy** leads to better maternal-placental health and improves some metabolic outcomes in the fetal offspring

Future studies will determine if fetal adaptation to maternal diet switch improves overall health

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